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APRIL 1942

DETERMINING FACTORS IN THE END-RESULTS FOLLOWING WAR WOUNDS AND COMPOUND FRACTURES*

H. WINNETT ORR

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THERE was a short period in the history of surgery when we could be and were quite definite about our attitude toward compound fractures and compound fracture wounds. We did not treat the wound. The wound dressing was designed only to exclude infection. Unfortunately, this period was very short. I refer to the time about 1865 to 1870 when the true Lister method was proposed, described and employed by Joseph Lister himself.

In discussing wounds and compound fractures this evening, I shall first remind you that in order to deal successfully with this problem we must return, not to the technique or to the exact method of Lister, but to the Lister point of view. This original conception was described perfectly by Lister and was really comprehended by many of his pupils and contemporaries. Even a few of his successors were able to maintain the original Lister attitude toward wound infection. Generally speaking, those surgeons who adhered to the Lister ideal were few, while those who departed on various paths and in many directions were many.

* Read January 8, 1942 at the Annual Meeting of The New York Academy of Medicine.

As an illustration, I may quote from Dr. James L. Little (in 1877), lecturer on operative surgery and surgical dressings in the College of Physicians and Surgeons, New York:*

"We will turn our attention this morning to the subject of antiseptic surgery, a topic at present of universal interest and one with which, even should you never practice it, scientific medicine demands that you should be familiar. Professor Lister, accepting the germ theory, has applied to the treatment of open wounds an entirely new method which has so far yielded the most wonderful results. The principle of Lister's method is essentially this: In treating an open wound let neither the air, the instruments you use, your hands or the dressings that are to be applied, nor in fact anything come in contact with the wound unless it has been thoroughly saturated or wet with a solution of carbolic acid, and at the same time keep the wound thoroughly drained."

This was *not the principle* of the Lister method, only some of the details of the Lister technique from which Dr. Little and many others promptly departed.

Dr. Little continued: "Carbolic acid comes in crystals, but the addition of a little water dissolves them. You should procure two bottles; one that will hold a quart and one that will hold two quarts, and a two-ounce graduate. To 30 ounces of water add an ounce and a half of the carbolic acid and you have a solution of the strength of one part of carbolic to twenty of water. From the two quart bottle pour off four ounces and add the same amount of carbolic acid. You then have a solution of one part of carbolic acid to forty of water. Now you are ready to employ the Lister method so far as the solutions are concerned."(!)

Dr. Little described at the same time, the use of thymol which had been employed not very successfully by Dr. Weir. Dr. Little expressed the hope, however: "That some more pleasant antiseptic will soon be discovered to take the place of the disagreeable carbolic acid."

Dr. Little employed the spray and described its use in great detail. Then he said: "We will now turn our attention to the antiseptic gauze. This is made of very coarse muslin or cotton gauze sprinkled with a hot mixture of resin and paraffin and one part of crystallized carbolic acid. Another material which can be prepared in the same way or pur-

* From a *Series of Clinical Lectures*, Edited by E. C. Seguin, Vol. III, No. xi, p. 298. New York. G. P. Putnam & Sons, 1878.

chased from a dealer, is the mackintosh cloth or protective oiled silk."

Lister taught that a certain kind of safety pin should be employed with a guard protecting the point of the pin. He said that even a pin hole through the mackintosh might permit the entrance to the wound of enough germs to cause the death of the patient.

In 1877, however, both Lister and Dr. Little were advocating the use of rubber drainage tubes. These tubes damaged the wound surface and permitted the access of new infection to the deep recesses of the wound.

These inconsistencies—exposure for dressings with damage to the wound surface, and the drainage tube opportunity for infection, have led to many of our difficulties in the control of fractures and in the protection of the wound against secondary infection. They have led to pyemic and septicemic complications and have predisposed to inflammation, scar formation, disability and deformity.

In 1904 when I began the study of orthopedic surgery I was drilled by Dr. Ridlon in the teachings of Hugh Owen Thomas (even with regard to intestinal obstruction) but he never did ask me to read the writings of Lister. I had not read all of them until after the war of 1917-1918. It had been my impression that Lister's original writings were very much out of date. I was familiar with the fact that Lister had renounced the antiseptic method as far as the carbolic spray was concerned. I thought then, as I have found many other surgeons to think, that Lister had abandoned his original conception of antisepsis when he abandoned the spray.

As I re-read the writings of Lister in 1919, I found that he had, to an extent, receded from his original teaching as to the exclusion of infection. He did allow himself to be influenced by his colleagues and his contemporaries to begin the search for a less offensive chemical than carbolic acid and for one which might actually cure wound infection.

But while Lister had been led by Robert Koch and others to try mercurial antiseptics, he regretted a tendency toward careless chemical dressings as a substitute for exclusion. Chemical wound dressings and chemotherapy were not then and have never been the true Lister method.

It is this search for a chemical that will kill germs without harm to the patient that has done antiseptic and aseptic surgery much harm. For example, a British surgeon said in 1918: "In dealing with compound

fractures and compound fracture wounds it is important for the surgeon not only to defend against infection, but to know when to attack." But what many of us forgot in those days was that in attacking the infection we were often attacking the patient as well, and about the time that the infection and the germs were in retreat, the patient was about ready to surrender also.

We have all been misled, as Lister was, by the recovery of patients for whom certain kinds of antiseptic gauze or certain forms of chemical solutions were employed. We lose sight of the point that before the days of Listerism and in spite of some of the revolting wound treatments that were then employed, patients got well in spite, rather than because of the surgeon's efforts.

Many of our correct ideals with regard to treatment of wounds and fractures were inherited from Hunter, Hilton and Hugh Owen Thomas. In a period in New York surgery fifty years ago tuberculosis of the hip or morbus coxarius was being treated by machines or apparatus designed to provide immobilization and traction for the hip. After many years of travail, during which the Sayre, Washburn, Stephen Smith, Hutchinson, Bauer, Shaffer, Duncan Eve, Wyeth, Stillman and Roberts splints were devised, manufactured and applied, we came to the point where real immobilization and rest were obtained by the Thomas splint, much simpler, lighter in weight, more efficient and less expensive; or by the plaster-of-paris cast. During those days we had advocates of radical surgery, motion, ambulation, and even chemotherapy for tuberculous joints—but no more.

We know that rest rather than radical surgery or medication will assist patients to recover from tuberculous bone and joint disease.

But we have not made so much progress in the matter of compound fractures. There have been too many attempts to individualize therapeutic technique and apparatus for different patients, different occasions and especially for different splints and surgeons to arrive at standard methods, continuity, or systematic treatment.

A common admonition of surgeon-teachers is that the surgeon on the spot in an emergency must decide the special apparatus, methods, and program appropriate for any patient. Every surgeon should have in mind that certain fundamentals, such as, restoration to normal position, immobilization, control of hemorrhage, and protection against further trauma and infection are essential and should always come first.

In acute infections even more than in chronic bone and joint disease, immobilization and rest are necessary to avoid or reduce inflammation, scarring and subsequent fixation, adhesions and ankylosis.

We do not seem to have arrived at this "rest" point of view for the acutely inflamed fractures and compound fracture wounds. There is still the attempt to diminish the amount of apparatus, to provide more joints and mobility, to make our patients ambulatory and to render less efficient rather than more so the kind of control which Thomas described long ago as rest "enforced, uninterrupted and prolonged."

We should not forget that scarring, stiffness and disability in the vicinity of fractures are brought about by improper motion, inflammation and irritation just as they are in tuberculous joint disease.

When I began my infrequent-dressing and rest method for osteomyelitis, infected wounds and compound fractures about twenty years ago, I had become convinced that the Carrel-Dakin, Willems, and Blake teachings, and primary and secondary suture were all doing much harm. My feeling arose partly out of realization that the teachings of Lister, Hilton, Hugh Owen Thomas and Ridlon regarding infection and rest were being violated. I believed firmly *that wound surfaces should be protected, that infected wounds of any degree should be drained, that all fractures should be reduced and immobilized, and that any injured or inflamed limbs should be protected against muscle spasm and other painful movements.*

A very few clinical trials were sufficient to convince me of the correctness of these assumptions. Many years of further clinical experience have assured me that these fundamentals are correct but that other details of treatment are often incidental and unnecessary.

My own results have been obtained without sutures, without drainage tubes and without antiseptic wound dressings. Sometimes cures or results attributed to chemical agents or "modified" techniques have been attributed wrongly to them, when better immobilization, rest and protective methods have given the patient his own chance to recover.

I could quote many reports from recent literature to illustrate this point. Perhaps one from a New York surgeon will be sufficient. In Bone and Joint Surgery for October, 1941, he says: "I have recently treated 45 fractures of the tibia by open operation. The results in all 45 cases have been good, though recovery in one or two was somewhat delayed. To date there has been no loss of life or limb attributable to

the open method despite the fact that as yet none of the newer drugs, such as sulfanilamide has been used as a prophylactic against infection." I am not quite sure whether this New York surgeon is being naive—a term sometimes reserved for those of us from the provinces—or whether he is "pulling our leg."

In this connection we might do well to recall what Dr. Flexner said in his book on "Medical Education": "There is a wide-spread impression that the scientific quality of medical practice is dependent upon the part played by the laboratory. This is not the case." Clinicians especially are inclined to regard the laboratory worker as always scientific and more or less infallible. It should be remembered, I think, that mistakes as to cause and effect, so often attributed to the clinician, may be made by the laboratory worker too, especially if he tries to carry his methods and conclusions into the field of practice.

It is interesting that in recent months a piece of research has been carried out which has had the effect of rationalizing completely all of our contentions regarding the importance of immobilization and rest in the treatment of inflammation and infection. This work was done, in part, by Dr. Trueta who made such a fine contribution to the plaster-of-paris cast and infrequent-dressing method by his work in Barcelona during the Spanish War. Dr. Trueta has recently been at Oxford, England, and has conducted a study with Dr. Barnes of Oxford on the influence of immobilization upon the lymphatic circulation in the extremities.

Barnes and Trueta published in the *Lancet*, London, May 17, 1941, page 263, an article on the absorption of various toxins and other materials from the mesenchymal tissues under circumstances similar to those in wounds and compound fractures.

Barnes and Trueta tied off the lymphatic circulation in animal limbs and introduced certain organisms into the tissues. They found that with the lymphatics obstructed, very few of these organisms got into the blood or into the spleen. Also, even from recent wounds, very few organisms were taken up by the freshly injured blood vessels, but such as were carried into the body of the animal at all, were taken by way of the lymphatics.

Snake venoms, some of which were so poisonous that they would kill animals in ordinary ways within ten minutes, could be excluded from the body of the animal generally by obstruction of the lymphatic circulation in the poisoned extremity. As soon as the ligated lymphatics

were relieved, however, even after an hour or so, the poison which had been held in the extremity by this ligature, escaped into the body and the animals promptly died.

Another experiment had to do with the reduction of the lymph flow by physiologic means. Rabbits had their lower extremities completely immobilized by means of plaster-of-paris double spica casts. Then snake venom was injected into the immobilized lower extremity, and one animal was found to be perfectly well after 105 minutes; then the plaster was removed and the animal allowed to move the limb about and died within seven minutes. A second animal remained in plaster for 210 minutes and died 60 minutes after the removal of the cast.

One method by which edema may be prevented, Dr. Trueta says, is by the enclosure of the injured parts in a plaster cast. The reduction of the lymph flow obtained by this means is further enhanced *if local drainage of the inflamed parts is provided by incision.*

The support adduced, by Dr. Trueta's research, for the immobilization and skeletal fixation of these extremities in plaster-of-paris is of the greatest importance. It has an important bearing on the immobilization and rest treatment of all infected wounds and fractures. It not only explains the excellent results we have obtained by this method, but points the way to further study along this line.*

I wish to refer briefly to the report of the Committee on Fractures and other Traumas published in *Surgery, Gynecology and Obstetrics*, November, 1941. This resolution was adopted at New Orleans last January. The conclusions of this Committee may be summarized as follows:

1. The use of snug-fitting plaster encasements in initial treatment of acute compound fractures is inadvisable.

2. Early splinting, utilizing fixed traction, should be followed by adequate debridement at the earliest possible time.

3. Wounds of the soft parts, not involving bones, joints, nerves or tendons, may be closed by secondary suture when bacterial checks in the laboratory prove that closure of the wounds is permissible.

My answer to these three proposals in general is that they represent the point of view that prevailed during the War of 1914-1918. That our results then were most unsatisfactory no one now attempts to deny.

With regard to the use of plaster, thousands of surgeons are now prepared to assert that properly applied plaster-of-paris casts may and

* At this point slides were shown to demonstrate the technique of skeletal traction, fixed traction in casts and tables showing clinical results.

should be used immediately after compound fractures. If such fractures are reduced, if the limb is put in the cast in correct length and position and if the wound is protected against secondary infection, this represents, to many of us, ideal treatment (which permits transportation) under any circumstances.

With regard to temporary splints and secondary debridement, this involves secondary trauma to the wound, disturbance of the limb and the patient, and revision of the fracture. Many of us feel that such treatment is quite wrong. Primary reduction, direct or indirect fixation in plaster-of-paris casts and with no change for several weeks is much to be preferred. This method is in extensive use here and in war areas abroad.

With regard to the closure of wounds, there are practically no such wounds such as those described by the Committee as suitable for primary or secondary closure. We are not much concerned about abrasions and skin wounds, but for those which do involve tendons, joints and bones, more important surgery, operative and postoperative, primary and secondary is required.

The outline of treatment proposed in the Committee's report is an outline which was carefully considered, thoroughly tried and largely discarded after our military experience twenty years ago.

One of the common misconceptions with regard to the infrequent-dressing method is that the patient is likely to become septicemic, pyemic or toxic as a result of foul smelling dressings or casts. That a bad odor is a necessary concomitant of this method is an entirely erroneous idea. Such wounds and discharges as do have bad odors, have them because of contamination with certain saprophytes that occurs at the time of injury, at the time of operation, or quite often because of careless secondary dressings. In most of our cases, whether of wounds or compound fractures, no postoperative odor is associated with the case at all. The patients we receive late, after they have been contaminated already, are sometimes difficult to clean up and for a time may have disagreeable odors. Even such cases, however, can usually be kept clean and dry so that the odor disappears. Then they make a satisfactory convalescence without further difficulty from odor or otherwise.

Another misunderstanding as to skeletal fixation is that the primary reduction and fixation of the limb must undergo revision and readjustment if it is found that the fracture surfaces are not perfectly approxi-

mated. Spaces between the ends of the fractured bones will fill in with callus and bone repair if they are truly immobilized in correct position and are undisturbed during convalescence. No delay in union is to be anticipated even if the fragments are slightly separated.*

A diversion that is a common cause of inefficiency in fracture treatment arises out of the idea that the patient will be better off if he is made ambulatory. There is seldom any justification for trying to get a leg or femur fracture patient on his feet. As for moving joints in the vicinity of fractures, this is still as wrong as it was before skeletal fixation was invented. Certain complications, such as localized infection, failure of union and even stiffness of joints are much more likely to occur in any ambulatory fracture patient.

A final point that I should like to emphasize is that it is seldom necessary to experiment upon the patient with new methods or techniques. It is quite possible to decide upon theoretical grounds whether a new treatment is likely to do more harm than good. If a proposed treatment is inefficient for fracture reduction, if it fails to provide or prevents adequate drainage of an infected wound, if there will be motion or muscle spasm or pain in a fracture area, if the fracture must be readjusted after reduction, or if the wound must be traumatized or exposed to reinfection, the new method is probably not worth a trial. It will usually be better to adhere to the methods we now have and that do not neglect or violate the fundamentals of reduction, asepsis, drainage, immobilization and rest.

It is always the duty of the surgeon, not only to provide proper conditions for recovery, but to protect the patient, as far as possible, against his own voluntary, or involuntary, violations of the treatment regime, or other indiscretions.

* The contention that the ends of the fragments separate because of absorption and must be brought together by secondary adjustment is also wrong. If the fragments are in correct position and truly immobilized from the beginning, absorption at the ends will not occur.

EVALUATION OF DRUGS USED IN THE TREATMENT OF CARDIOVASCULAR DISEASES*

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To make an evaluation of all drugs used in the treatment of heart diseases in the time allotted to me is obviously impossible. Since I cannot cover the whole field, I will limit myself to those problems in drug therapy that seem to me to be of greatest interest. Drugs are, of course, not the only forms of treatment used in cardiology. Bed rest, diet, nursing care, physical therapy and, not the least, psychotherapy, all play important roles in the management of any patient with heart disease. Thus, in discussing certain phases of drug therapy tonight, I do not want to leave the impression that other therapeutic measures are either unimportant or unnecessary.

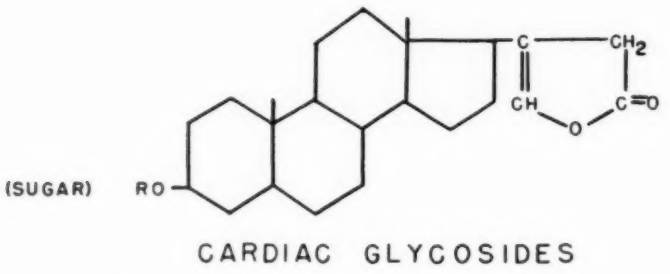
In presenting treatment from the standpoint of the drug rather than that of the patient we are not following the usual pattern. The point of view is that of a pharmacologist rather than that of the clinician. Although as a general rule this method of presentation is the least desirable, still there are certain advantages in so doing occasionally. A doctor is inclined to get lazy in his thinking after the diagnosis is made, and he may then prescribe potent remedies without having any more knowledge of the underlying actions and potential dangers of these drugs than the patient has to whom he is giving them. The doctor thus needs these facts brought to his attention, and an occasional review of basic pharmacology is desirable. I would suggest that a good textbook of pharmacology of recent vintage be available for ready reference on every doctor's bookshelf.

Digitalis is still one of the most important drugs used in the treatment of diseases of the heart. Its chief use is in the treatment of congestive heart failure, although it can sometimes be used to control the rapid ventricular rate of auricular fibrillation when heart failure is not

* Read before the Graduate Fortnight at The New York Academy of Medicine on October 16, 1941.

present, and to reduce the number of ventricular premature contractions when they are bothersome. It would seem hardly necessary to take up much time on digitalis except for the fact that some interesting developments have occurred in the last few years. We need not discuss the importance of controlling the use of digitalis by a preliminary period of bed rest until weight is constant, and after digitalis is given by noting the weight loss, by charting the ventricular rate in the case of auricular fibrillation and by noting daily the changes in the patient's symptoms and physical signs; nor is it necessary to point out that the initial digitalization must be made rapidly so that the concentration of digitalis in the body will be built up rapidly. I will leave the familiar aspects of digitalis therapy, therefore, to discuss two important developments in the digitalis field. These have occurred in the matter of bio-assay and in the use of the pure glycosides to replace the powdered leaf and the tincture.

The U. S. Pharmacopoeia in the Twelfth Revision has finally adopted the cat method of assay as official and the monograph is now in the process of being written. For many years clinicians have known that preparations of digitalis standardized on the cat are much more reliable than those standardized on the frog. Quite recently Gold et al[1] have shown by direct studies on man that the assay on the cat more closely approximates the values that we want than the assay on the frog. After all, the only purpose of a biological assay is to give us some indication of the possible potency in man. If the assay does not do this, as it apparently did not do with the frog, the assay is valueless. The term "cat unit" should be discouraged because the unit which will be established is not an absolute unit based on a lethal dose for a cat, but is a comparative unit based on the results obtained by cat assay on an unknown in comparison with a simultaneous cat assay on the standard pharmacopoeial digitalis powder. "Digitalis unit" will be the only term used regardless of the method of bio-assay. All preparations of digitalis should be checked on man because even the cat assay, although closer than the frog, may occasionally be off, particularly if the digitalis contains an unusually large amount of a slowly eliminated fraction. The suggestion has been made that all assays should be made in man and that the changes produced in the electrocardiogram should be used as the endpoint. However, anyone who has had a reasonable amount of experience with the effects of digitalis on the electrocardiogram will



CARDIAC GLYCOSIDES

Fig. 1. Chemical Structure of the Cardiac Glycosides

know that there is no constant relationship between the therapeutic and toxic doses of digitalis and the electrocardiographic changes. Recently a carefully controlled study by Geiger, Blaney and Druckemiller[2] caused them to come to the conclusion "that the electrocardiogram has no practical clinical value for the quantitative estimation of digitalis saturation of patients." They found that the depression of the ST segment and diminished amplitude of the T waves occurred in less than one-half of the electrocardiograms of digitalized patients and that the onset and progression of such changes, when they did occur, were unrelated to the amount of digitalis that had been given. It is only in very carefully selected patients that the ventricular rate in auricular fibrillation can be used for comparative digitalis studies, and then the conclusions must be drawn only with extreme caution. The ventricular rate in some patients with auricular fibrillation may fall to normal on bed rest alone. Other patients who have had a rapid ventricular rate before digitalis, on digitalization develop a slow rate and then, in spite of the fact that no digitalis is given for several weeks, the ventricular rate does not return to the original level.

Since the cat assay, even though it is better than the frog assay, occasionally gives false information as to the anticipated potency in man, search is still being made for a better method of bio-assay. Let us hope when such a method is found it will not take a twenty years' fight to make it official. A method which looks promising is the embryonic chick heart assay method, first described by Paff[3,4] and now being investigated in our laboratory. It has the advantage of lower cost, shorter time for the assay, and greater availability of biological material.

In the meantime, investigation on the pure glycosides found in digitalis and other related pharmacological substances has progressed to the point where it would appear that eventually these pure substances will entirely replace the crude drug and the need for bio-assay will no longer exist.

The chemical structure of the cardiac glycosides is interesting in that it contains the sterol nucleus which is common to the estrogens and androgens, corticosterone, vitamin D and cholesterol (Figure I). The occurrence of this nucleus, particularly in common with the hormones found in the body, naturally arouses interesting chemical speculations. The butyro-lactone ring is contained in the basic structure of the genin or aglucone. Variations in the genin occur with various substituent groups on the nucleus. The desoxy sugar is attached at number 3 position. The term "glycoside" rather than "glucoside" should be used because a desoxy sugar is always present and glucose is frequently absent and, furthermore, if present, is not essential for the glycoside action.

Many modifications are possible both in the genin and in the attached sugars. Thus, when we speak of cardiac glycosides we speak of chemically related and not identical substances. Like the series of amines related to ephedrine, where variations in action are noted, for example between ephedrine and neo-synephrin, we must expect variations in the actions of the individual cardiac glycosides. There are differences in rates of absorption, differences in rates of elimination, as well as other pharmacological differences. The cat assay is particularly unreliable when applied to the cardiac glycosides. For instance, a patient can be maintained on about one-quarter the cat assayed amount of Digitoxin as he can on powdered leaf. It is important, therefore, to learn the dose of each glycoside in terms of mgm. actual weight and not in bio-assay units.[5]

Mercurial diuretics are firmly established as essential drugs in the treatment of congestive heart failure not responding to digitalis. Dyspnea alone in the absence of edema has been shown to be relieved by the use of mercurial diuretics as shown by the vital capacity studies of Alsever and Levine.[6] Fluid accumulations due to cirrhosis of the liver, thrombophlebitis, or abdominal neoplasms may be diminished by this form of therapy.

The necessity for the combination of theophylline with the mercurial salt is now thoroughly recognized. Manufacturers have followed

TABLE I

COMPARATIVE EFFECTIVENESS OF MERCURIAL DIURETICS WHEN ADMINISTERED BY THE ORAL, PARENTERAL AND RECTAL ROUTES

Diuretic	*Number of trials*	*Trials successful*		*Number of patients*	*Patients successfully treated*	
		Number	*Per cent*		*Number*	*Per cent*
Salyrgan-Theophylline by mouth (5 tablets)	56	40	71.5	29	22	75.8
Salyrgan-Theophylline intravenously	37	35	94.6	24	23	95.8
Mercupurin intravenously	60	55	91.7	30	29	96.6
Mercurin suppository	22	14	63.6	13	6	46.1
Salyrgan (modified) suppository	20	10	50.0	11	8	72.7

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the lead of mercupurin, the first mercurial diuretic to contain theophylline chemically combined with the mercurial salt. When originally introduced, the theoretical reason for the combination was that there was produced a more potent diuretic by the synergistic action of a mercurial with a xanthine. The effect was obtained, but not for the reason assigned by the original investigators, Issekutz and Vegh.[7] The presence of theophylline in molar equivalents to that of the mercurial salt has been shown to prevent necrosis at the site of injection.[8] Furthermore, the increase in diuresis over that of the simple mercurial was due to more rapid and complete absorption.[9] Sloughs and ulcers, gangrene and other serious local complications formerly found as a common occurrence with the injection of mercurial diuretics are now exceedingly rare.

Although methods of administration other than by the intravenous or intramuscular route are now used, none are quite as effective (see Table I). The intravenous route is almost 100 per cent effective. At the time this table was made we had just completed our study on salyrgan-theophylline tablets administered by mouth to hospital patients with large amounts of edema.[10] The results looked very promising. Subsequent studies on ambulatory patients, however, were not so encouraging. It would appear that the less retained fluid there is, the higher is the incidence of undesirable side actions, particularly gastrointestinal irri-

tation. It is our present opinion, therefore, that only in an occasional ambulatory patient is it desirable to use the tablets orally. The suppositories seem to be tolerated much better.

The possible toxic effects on the kidney are well known and should be watched for. The presence of increasing albumin, casts or a greater number of red blood cells are danger signals. Very rarely a patient may suddenly go into shock or even die shortly after an intravenous injection of a mercurial diuretic. This accident is fortunately very rare. Animal experiments have shown that sudden death shortly after the administration of a mercurial diuretic intravenously is probably due to ventricular fibrillation. Some mercurial diuretics produce this more readily, and with smaller doses than others. All mercurials, however, can give this effect if a large enough dose is used and injection is sufficiently fast. Two notes of caution are, therefore, to be considered in intravenous injections:

1. Never use more than 2 cc.
2. Draw up blood into the syringe before injection and then take plenty of time to inject.

Mercurial diuretics work more effectively if ammonium chloride, ammonium nitrate, urea, potassium chloride or other salts which in themselves have diuretic properties are given at the same time. Ammonium chloride in enteric coated capsules is probably the most convenient form and the one best tolerated by the patient.

One cannot well leave out of this discussion drugs used in the treatment of the anginal syndrome, since this condition is so common. Departing for the moment from our set plan to discuss drugs only, we might briefly review the important points in treatment.

First and foremost is the necessity for a correct diagnosis. Every pain in the chest is not the anginal syndrome. Second, the anxiety factor is prominent and psychotherapy is, therefore, necessary. Third, supportive treatment is often more important than so-called specific therapy. This includes the use of sedatives. Also might be mentioned the relief of flatulence by some member of the atropine group, of which novatropine is probably the best example. Fourth is specific therapy directed towards dilating coronary arteries. The main drugs in this group are the nitrites and the xanthines.

Of the nitrites, nitroglycerine is still pre-eminently the best. The nitrites relax all smooth muscle, for instance in the bronchi, in the biliary

tract and in the intestine, if spasm is present. Relief of pain, therefore, when nitroglycerine is used does not presuppose the presence of coronary artery disease. The longer acting nitrates, such as erythrol tetranitrate and mannitol hexanitrate, have a limited use because many patients develop side actions.

The greatest controversy at present exists over use of the xanthines, particularly aminophylline. It might be well to review briefly the evidence for and against their use.

In a perfused rabbit's heart Fowler, Hurewitz and Smith[11] found that aminophylline caused greater and more consistent increase in coronary flow than any other member of the xanthine group. These observers also found that the drug when given by mouth to dogs after ligation of a coronary artery promoted an extensive collateral circulation. Wiggers and Green,[12] also working on dogs concluded from their experiments that "an increase in collateral circulation sufficient to be of functional use cannot be attained by use of vaso-dilating drugs after complete coronary occlusion." Gold, Travell and Modell[13] ligated various coronary arteries in cats and then found that intensive use of aminophylline for three weeks produced no effect on the systemic blood pressure, or the course of the electrocardiographic changes nor did it reduce the size of the infarct. The weight of experimental evidence would indicate that little if any increase in coronary bloodflow would result from the use of aminophylline. However, in man, Levy, Bruenn and Williams,[14] using induced anoxemia in patients subject to attacks of cardiac pain caused by coronary sclerosis, found that aminophylline injected intravenously caused a prolongation of 63 per cent in the time of appearance of pain. At the same time RS-T deviation was diminished by 58 per cent. When aminophylline was taken by mouth, there was a prolongation of 26 per cent in the time of the appearance of pain and the RS-T deviation was diminished by 32 per cent. This work would suggest some coronary artery vasodilation by aminophylline, more pronounced when given intravenously, but still noted in one-quarter of the patients when the drug is given by mouth. Riseman and Brown[15] studied the effect of xanthines and other drugs on patients with the anginal syndrome using the exercise test as an objective method for measurement. They found that one-half of the patients were benefited by aminophylline if a large enough dose were used. However, clinical tests controlled by placebos have shown that aminophylline or other xanthines have no superiority

over the placebos.[16, 17, 18]

It is evident then that there is considerable doubt as to whether or not aminophylline is of value as a coronary vasodilator in man. However, no investigator has found the drug to be dangerous, when given by mouth, so it can, therefore, be safely assumed that even though the aminophylline may do the patient no good, it can certainly do him no harm.

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TREATMENT OF LEUKEMIA BY RADIOACTIVE PHOSPHORUS*

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LEUKEMIA presumably arises more or less focally, as in marrow or lymph nodes, and only subsequently progresses to involve other tissues than those normally concerned in the production of leukocytes. Nevertheless, as observed clinically in the human subject, it is invariably a generalized disease. Thus, it is not at present conceivable that any method of regional treatment can do more than palliate by causing regression of the main symptom-producing foci.

Yet the method of treatment chiefly relied on in the past three decades for the palliative treatment of leukemia has been local irradiation, especially by x-rays. This has been a natural consequence of the discovery that leukemia is a radiosensitive process, and of the gradual development of roentgen therapy as applied to various neoplastic processes.

While striking remissions can be caused by suitable local irradiation, directed to spleen, lymph nodes, bones, or other sites of leukemic infiltration, admittedly this focal attack is at best only an expedient, and leaves much of the disease untreated, so that eventually the process as a whole progresses beyond control and the patient dies. Statistical studies of results of local irradiation for leukemia show that there may be at best a lengthening of duration of survival by only a few months, although undoubtedly during the patient's remaining span of life he may secure notable remissions which otherwise he could not hope to have. While the occasional patient may survive for ten years or more, most of them die within three years. About 6 per cent of patients with chronic myelogenous leukemia and about 9 or 10 per cent with chronic lymphogenous leukemia survive five years from the beginning of treatment.[1]

Recognizing the fallacy of attempting to control leukemia, a generalized disease, by local irradiation, numerous workers, particularly in

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the past decade have sought to treat the disease in toto by so-called spray irradiation of large segments of the body or by total body irradiation. These methods bring about a nearly uniform distribution of radiant energy throughout large segments of the body or the whole body. To be effective in palliation, the dose must be kept within the limits of the patient's tolerance, and at the same time must be sufficiently great to have an appreciable effect on the radiosensitive leukemic tissues. The principle on which this irradiation of all the body tissues is based is the differential in radiosensitivity between leukemic and normal tissues. While notable palliations are observed in many instances in the treatment of leukemia by spray or whole body irradiation, the obvious limitation lies in the fact that the patient's tolerance of whole body irradiation is nowhere near sufficiently great to permit taking full advantage of the differential in sensitivity between leukemic and normal tissues.

If, then, it became possible to deliver radiant energy in considerably higher concentration to the leukemic tissues which are usually more radiosensitive than the normal cells, the damage done to the leukemic tissues would be greater than to the normal tissues, and therefore we would approach a more nearly ideal method of treatment of leukemia by irradiation.

This ideal seems to be approached by radioactive phosphorus therapy. Yet it is necessary to keep in mind that treatment of leukemia by radioactive phosphorus is simply another method of whole body irradiation, and that probably it will be found sooner or later that no form of irradiation is the answer to the problem of the treatment of leukemia.

Phosphorus Metabolism in Leukemia

The importance of phosphorus as an element in the metabolism in leukemia is emphasized by Forkner[2] as follows:

"In chronic leukemia, untreated or not recently treated, there is usually a marked elevation of the blood phosphorus due to the total phosphorus content of cells, especially immature white cells. The phosphorus of the plasma varies greatly but remains within normal limits.

"Treatment of leukemia with roentgen rays or by means of radium results in a further increase of organic phosphorus in the blood and a transitory marked increase of organic phosphorus in the plasma, these values returning to normal as the patient is benefited and as the leuko-

cytes approach normal values in the blood.

"No variations of inorganic phosphorus occur in the plasma or cells before, during or following treatment with roentgen rays."

Studies made within the past year by Abels[3] at Memorial Hospital of the post-irradiation changes in the organic phosphorus in the blood of patients with leukemia showed a marked agitation of organic acid soluble phosphorus levels in the leukocytes and usually in the erythrocytes after administration of radiation by any one of three methods: radioactive phosphorus, precordial x-ray therapy, and whole body x-ray therapy. The administration of non-radioactive phosphorus was not followed by significant alterations in phosphorus content of the blood cells.

Lawrence and his co-workers[4,5,6] of the University of California have shown both in mice and in humans that radiophosphorus given in the form of sodium phosphate concentrates at first in the bone marrow and those tissues infiltrated with leukemic cells, and later concentrates in the osseous tissues.

Tracer studies made at Memorial Hospital by John Kenney[7] have confirmed the fact that leukemic tissues pick up radioactive phosphorus in greater concentration than do normal tissues. What we term the differential absorption ratio for various tissues is determined as follows:

The amount of P-32 actually present in a given weight of a particular tissue as determined by measurement by means of the Geiger counter is divided by the amount of P-32 that would be present in the same weight of tissue were the administered amount, corrected for decay, evenly distributed throughout the body. In this manner it has been found that while normal lymph nodes show a differential absorption ratio of from 1.2 to 2.2, lymphosarcomatous or leukemic nodes show a differential ratio of from 2.2 to 12, averaging about three.

The factor of loss of active substance is also of great importance, loss by failure of absorption, by excretion, and by decay of radioactivity. Loss in the stools during the first four days after administration of an oral dose of P-32 depends on the amount given, and may total from less than 20 per cent to as much as 50 per cent. After the first four days the daily loss in the stools is less than 1 per cent of the retained body dose. Urinary excretion during the first 4 days totals about 10 per cent of the administered dose, and thereafter averages less than 1 per cent of the retained body dose per day.

The rate of disintegration of the radioactive material is also impor-

tant. Since the half-life of P-32 is 14.3 days, it follows that in three weeks 75 per cent of the administered material has decayed.

Taking into account these sources of loss, it is obvious that in three weeks very little activity remains. Thus there is little fear of unduly prolonged radiation effects from P-32.

Radioactive phosphorus or P-32, like other artificially produced radioactive isotopes, is a product of the cyclotron or so-called atom smashing machine. Ordinary red phosphorus with an atomic weight of 31 is bombarded by nuclei of heavy hydrogen (deuterons) moving at a high velocity (energy 16 million electron volts). The result is that about one in every million atoms of the red phosphorus is converted to radioactive phosphorus with an atomic weight of 32 (hence the term P-32). The following equation presents the reaction:

$$_{15}P^{31} + {}_{1}H^{2} \rightarrow {}_{15}P^{32} + {}_{1}H^{1}$$

(red phosphorus) (deuteron) (radioactive phosphorus) (proton)

P-32 disintegrates at an exponential rate. Its "half-life" is 14.3 days, that is after every 14.3 days there remains only 50 per cent of what was present at the beginning of that period. The end product of the disintegration of P-32 is sulphur, $_{16}S^{32}$.

P-32 is measured in millicuries, as is radon (radium emanation), based on the number of atomic disintegrations per unit of time. When a sample emits 3.7×10^{7} beta particles per second it is said to contain one millicurie. It is a peculiar and probably fortunate property of P-32 that its disintegration causes the emission, not of alpha and beta particles and gamma rays as does radon, but only of beta particles, which have a penetrating power in tissue of only about 2 mm. on the average.

It is estimated, for purposes of comparison with x-ray therapy, that 1 millicurie retained for twenty-four hours by an adult of 70 kg. weight, would deliver the equivalent of 0.6 roentgens of whole body radiation.

Through the courtesy of John H. Lawrence of the University of California we have received at Memorial Hospital for the past 2 years regular shipments of an aqueous solution of dibasic sodium phosphate containing about 15 milligrams of phosphate per cc. of solution, representing a mixture of radioactive and inactive phosphorus. (About one in every million atoms of the phosphorus is radioactive.)

Upon receipt each shipment is re-measured for its radioactivity per cc. It is then a simple matter to measure out from day to day individual doses as requisitioned, making of course, proper correction for the rate of loss by disintegration.

P-32 may be given orally, intravenously, or by other parenteral routes.[8,9] We have used the oral route almost routinely. In some instances we attempted intravenous use of the solution sterilized by boiling after its receipt in New York, but found such an incidence of reactions evidently due to some pyrogenic substance that we felt it unsafe to continue intravenous administration, unless the material were to be made sterile at the source. The only disadvantage of the oral route is that about 25 per cent is lost through the feces.

Dosage of P-32 in Leukemia

In the beginning of our work with the treatment of leukemia by P-32 we used fairly large single doses at intervals of about a week. However, certain evidence has accumulated that has led us to believe it preferable, after evaluation of the patient's status, to select a certain dose related definitely to the patient's body weight and to divide this dose into 5 to 7 fractions, to be administered one a day. This division of dosage apparently reduces the excretory loss of phosphorus and probably favors a more complete pick-up by the leukemic cells.

The evaluation of the patient's status is fully as important if not even more so, as in selection of dosages of conventional radiation. The general condition of the patient, the degree of acuteness or chronicity of the leukemic process, as reflected by both clinical and hematological findings, and in particular the degree of remaining erythropoietic activity in the marrow, as estimated by sternal puncture, are the main factors considered in deciding what dose of P-32 to give.

To an adult in good general condition with chronic leukemia, and with evidence by sternal puncture of good erythropoiesis, the first total dose may amount to 70 to 100 microcuries per kg. of body weight. Thus to such an adult weighing 70 kg. a total of 5 to 7 millicuries may be administered in fractions of about 1 millicurie given daily for five to seven days.

To an adult in less favorable condition, with evidence of a more acute process, or with reduced erythropoiesis, the total dose to be administered in the first course may be reduced to as little as 20 microcuries per kg.

When trials are made of the use of P-32 in acute leukemia in children, we favor great caution in dosage, just as with conventional x-ray therapy.

In any less favorable case it seems advisable to begin with a single test dose, and observe the patient for two or three days to see what reaction if any is induced.

Depending on the response to the first course, subsequent courses may be given, usually in somewhat smaller dosage, leaving an interval of 1 to 2 weeks between courses. It is impossible to give any definite figure as to optimum total dosage.

Erf, Tuttle, and Lawrence[4] state that their first doses were determined by the following considerations:

"The lethal dose of radio-phosphorus for a 20 gram mouse is approximately that amount given intraperitoneally which emits 70 microcuries of beta-radiation; for a 6 pound monkey, 7 millicuries by the same route. These results suggest that the lethal dose of radio-phosphorus for an average adult human would be well over one hundred millicuries."

Their figures for single lethal doses in animals may be computed to work out to 3500 microcuries per kg. for mice and 2600 microcuries per kg. for monkeys. For a 70 kg. adult their estimate of 100 millicuries would be a conservative one of only about 1400 microcuries per kg. However, I believe it should be noted that any estimate of a lethal dose of radiation for a normal animal or human may need to be considerably modified when applied to a leukemic patient.

It would seem safer, for the present, to regard P-32 as a palliative, as another form of whole body irradiation. Many situations arise in cases treated by P-32 suggesting the addition of conventional local x-ray therapy. For example, when a patient who has had some treatment by P-32 shows a decrease of erythropoiesis in his marrow, but still has a large spleen or masses of nodes that have not satisfactorily regressed, suitable doses of local x-rays may be given such fields to advantage, with less risk of further depletion of the marrow than would be entailed by further P-32 therapy. It is noteworthy that the ingestion of radioactive phosphorus is not followed by symptoms of acute radiation sickness.

Results

From February 1940 to date*, thirty-eight cases of leukemia have

* November 18, 1941.

been treated by radioactive phosphorus. The follow-up is complete. These cases comprise twenty-two of the chronic type, fifteen acute, and one eosinophilic. The results may be summarized as follows:

1. Eleven cases of chronic myelogenous leukemia of adults.

Three died in 20.5, 4, and 4 months respectively following the beginning of P-32 therapy. All three appeared to have had a good result and to be under control until shortly before death. Eight are living, 11, 11, 9, 5, 5, 3, 1 and 1 month since treatment began. Of the whole group of eleven cases, seven, including the one who died after 20.5 months, showed definite evidence that P-32 is an effective therapeutic agent in this type of leukemia. In two there was no control, and two others have begun treatment so recently that nothing can be said about results in them. The total doses used in those who have been treated over any extensive period have been from 260 to 960 microcuries per kilogram.

2. Acute and subacute myelogenous leukemia, one case of each. Both patients died, one in one week and the other in six weeks, with no detectable effect of P-32, favorable or unfavorable.

3. Chronic lymphatic leukemia of adults, eleven cases.

On the whole this group has been less favorable than the chronic myelogenous cases, in that most of them were well along in their course and had had a considerable amount of previous x-ray therapy. Five died from two to ten weeks after P-32 was begun. One of these had so little treatment and for such a short time that his case could fairly be disregarded. Six are living, 12, 11.7, 10.3, 5.8 and 4.6 months.

Three or possibly four of the whole group of eleven have had real evidence of control of the disease by P-32; three living, 12, 11.7, and 10.3 months and one who showed some evidence of control but who died in two months, with splenic infarction.

The favorable effects seen in chronic lymphatic leukemia have been mainly the regression of enlarged spleens and lymph nodes, while in general the blood and marrow have not been notably influenced.

The doses for those for whom it was possible to give treatment for any considerable period were from 150 to 350 microcuries per kg.

4. Acute lymphatic leukemia of adults. Two cases, both in young women with no benefit from P-32, death occurring within a few weeks.

5. Acute lymphatic leukemia of childhood, eleven cases. Nine patients died in from one week to five and one-half months after P-32 was first administered. No real effect was seen in any of these, although

one, a five-year-old boy, who received 200 microcuries per kilogram, went home in poor condition, yet did improve for a time, and survived longer than we had expected, however, only 3½ months in all.

Two children are still living, one for three months, and still under treatment and having shown a slight effect on nodes; the other over four months and with a remarkable remission. In this case there was some discussion as to whether the result was that of sulfadiazene on an atypical acute infection with positive blood culture of hemolytic Staphylococcus aureus and a leukemoid picture, or a true remission of leukemia perhaps aided by P-32. A recent relapse, however, gives clear indication of the leukemic nature of his illness.

6. One case of eosinophilic leukemia in a girl of nine years, who also has rheumatic heart disease. She has survived six and one-half months since P-32 was first administered. She was treated from April 28 to July 19, 1941, receiving 260 microcuries per kilogram. On admission her white cell count was 134,600, with 90 per cent eosinophiles. Her spleen extended three fingers' breadth below the costal border and she had a slight general adenopathy. The red cell count was 3.7 million and the hemoglobin 56 per cent.

On October 16, her hemoglobin was 90 per cent, red cell count 4.2 million, white cell count 7,250, with 8 per cent eosinophiles. The nodes had disappeared, and the spleen was only one finger's breadth down. The liver remained very large, but she is a cardiac cripple and we believe the large liver mainly due to the cardiac condition.

Summary and Conclusions

1. Radioactive phosphorus offers a means of irradiation whereby leukemic tissue throughout the body may be somewhat selectively treated, without fear of undue retention of radioactive material. For purposes of rough comparison the method may be regarded as somewhat analogous to the Heublein or spray methods of whole body irradiation, with the possible advantages offered by the differential absorption ratio and the localized character of the P-32 irradiation.

2. P-32 is probably best regarded as simply another means of palliation for leukemia, and may be best used in many cases in conjunction with conventional local irradiation.

3. It is too early to attempt to compare the results of whole body irradiation by P-32 with those of spray irradiation by external sources

or Heublein therapy. However on theoretical grounds P-32 offers the advantage of more or less selective irradiation of leukemic tissues.

4. The results of treatment for leukemia have been as follows:

Chronic myelogenous leukemia. Excluding two cases whose treatment has been started in the past few weeks, seven of nine have shown clinical and hematological improvement.

Chronic lymphatic leukemia. In a rather unfavorable group of eleven cases, four at the most have shown a good response, by regression of spleen and nodes, without much effect on the blood or marrow.

Acute leukemias. Thirteen of fifteen have shown no evidence of favorable response. One survivor has been under treatment only three months and is still in a precarious state, while one has survived four months and has shown a remarkable remission, until very recently.

Eosinophilic leukemia. One case, with survival of six and one-half months, with remission attributable to P-32.

5. The study of the use of P-32 in institutions where control of dosage by accurate physical measurements is possible has not yet progressed to the point where it is safe to recommend the release of this potent agent for general therapeutic use.

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THE ADRENAL CORTEX AND ELECTROLYTE BEHAVIOR

Harvey Lecture, December 18, 1941

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THE gradual growth of knowledge concerning the functions and interrelations of the endocrine glands has undergone gratifying acceleration in the last two decades. This progress has resulted primarily from the integration of clinical and physiological studies which have gained both in scope and importance through the dramatic advances of organic chemistry. Identification and synthesis of the chemical compounds normally elaborated in the glands of internal secretion have furnished the clinician and physiologist alike extraordinary opportunities for controlled observation. The study of the effects of these various compounds in spontaneous disease and their action in pathological states arising from ablation of endocrine structures as well as the observation of their effects in intact animals has proved most profitable.

In the past fifteen years interest in the adrenal glands has been focused upon cortical function. It has become apparent that control of a number of significant and apparently quite dissimilar physiological activities is invested in the outer layers of the suprarenal capsules. These activities, hormonal in origin, are now known to include carbohydrate metabolism, electrolyte and water metabolism, and probably others. It is my purpose this evening to review primarily the role of the adrenal cortex in relation to electrolyte behavior.

The syndrome of salt loss and dehydration with its resultant state of shock is characterized clinically by progressive weakness culminating in overwhelming prostration, increasing pulse rate associated with falling blood pressure, subnormal body temperature, nausea and vomiting, sunken eyes, and loss of normal turgor of the subcutaneous tissues.[1] Examination of the blood in these states of dehydration reveals an increase in hematocrit and serum protein, i.e., decrease in water content, a decrease in bicarbonate or chloride content of the serum or a decrease in

both accompanying a fall in sodium. When the development of this syndrome is rapid there is also an increase in urea, which appears before the final stages of oliguria or anuria develop. The correlation of these clinical and chemical disturbances was first established in patients with cholera by O'Shaughnessy[2] in 1831. O'Shaughnessy also demonstrated that the intravenous administration of salt and water had a most salutary therapeutic effect. The similarity of the state of dehydration and shock in cholera to that in diabetic acidosis gave rise to the treatment of the latter condition by the intravenous injection of saline solution by Hilton Fagge[3] in 1874. Since that time the presence of the syndrome of dehydration and shock has been recognized in a number of conditions in which the physiological disturbance results primarily from the loss of inorganic base.

The interest of a group* at the Presbyterian Hospital in problems of adrenal physiology developed as a by-product of a long series of studies on electrolyte and water metabolism in normal individuals and in certain morbid states and was not initiated by a particular interest in the endocrine field. The obvious similarity of the syndrome of salt loss and dehydration to the familiar clinical picture of acute adrenal insufficiency in man, however, led us nine years ago[4] to make chemical surveys of the blood of a number of patients with Addison's disease. The abnormalities encountered were indeed striking and included a decrease in the sodium concentration of the serum with a corresponding drop in chloride and bicarbonate, an increase in potassium content of the blood serum, a variable increase in non-protein nitrogen, inorganic phosphorus and sulfate and calcium as well as hemoconcentration, i.e., decrease in plasma volume. Since that time we have had the opportunity of making similar observations in more than sixty patients with Addison's disease and the results obtained are in agreement with our initial findings and with those of Harrop,[5,6] Thorn,[7] Wilder,[8] and many others. Furthermore, they are analogous to those of Baumann and Kurland[9] made in 1927 in adrenalectomized cats.

The decrease in serum sodium concentration in the first three patients studied was impressive and in the third case, after the sodium had dropped under observation to 108.7 m.eq. per liter (Table I), the patient was treated with salt solution[10] following which she made a remarkable recovery, having literally been in extremis when therapy was instituted.

* Drs. D. W. Atchley, J. Stahl, J. W. Ferrebee, C. A. Ragan, Jr., D. Kuhlmann, D. Parker, and others.

TABLE I

CORRELATION OF BLOOD CHANGES WITH SALT FEEDING AND SALT WITHDRAWAL IN A PATIENT WITH ADDISON'S DISEASE

Date	*Na*	*K*	*Cl*	HCO_3	*Non-Protein Nitrogen*	*Blood Pressure*	*Remarks*
	m. eq. per l.	m. eq. per l.	m. eq. per l.	m. eq. per l.	mg. per 100 cc.		
July 19 1932	123.5	5.3	88.6	21.8	39.0	85/55	Blood taken shortly after admission. Profound weakness and vomiting.
July 26	107.8	7.1	72.7	21.5	45.0	65/48	Critically ill. Almost in extremis. No therapy up to this time.
Aug. 2	133.0	5.1	93.8	27.5	20.6	84/60	Treated with a single dose of Eschatin and then NaCl daily. No more vomiting, sitting up.
Nov. 14	139.9	4.6	107.3	24.3	20.0	112/74	Up and about at home, doing part of housework. Eats 7 gms. of NaCl daily plus diet. Slight puffiness of eyelids.
Jan. 24 1933	126.8	5.7	92.3	21.2	35.0	86/60	After 7 days salt-poor diet, weak and vomiting frequently. Confined to bed.
Jan. 30	138.0	5.0	103.5	25.9	25.0	122/80	After no further treatment except NaCl added to diet and given by rectum. No vomiting. Much stronger.

Subsequently, salt was withdrawn from the patient's diet with the result that a moderate crisis was precipitated in 7 days. Following the readministration of salt and water, the patient improved strikingly and was able to return home. The clinical improvement was associated with the correction of the chemical disturbances observed in the blood serum.

These observations demonstrated, among other changes, that (1) the acute adrenal insufficiency of Addison's disease is usually associated with a sharp decrease in the sodium content of the blood serum, (2) that the withdrawal of the sodium ion from the diet may induce acute adrenal

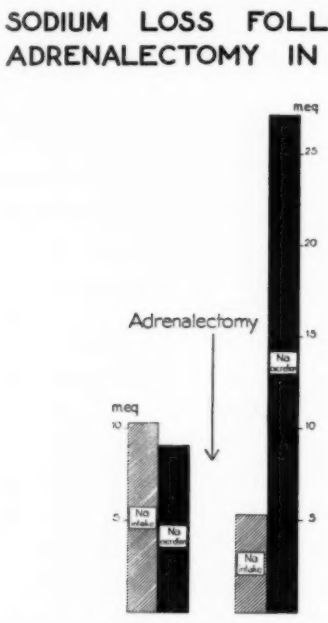

Fig. 1—Relation of sodium intake to renal sodium excretion before and after adrenalectomy. The great loss of sodium which follows adrenalectomy takes place through the kidneys.

insufficiency and that (3) this may be alleviated with correction of the various electrolyte disturbances by the readministration of salt and water. This is now an old and familiar story. Harrop, Soffer, Nicholson and Strauss[11] and also Allers[12] subsequently demonstrated that adrenalectomized dogs may be maintained in relatively good health for many months without the use of cortical extract, if given large enough amounts of sodium chloride to which is added sodium bicarbonate or citrate.

The next step in these studies was concerned with the mechanism by which the sodium concentration of the serum is reduced in adrenal insufficiency. For this purpose we studied in dogs the effects of adrenalectomy upon electrolyte balances as well as upon changes in serum electrolyte concentrations.[13] Upon removal of both glands, the familiar chemical pattern of the blood in acute adrenal insufficiency appeared and this, among other changes, was associated with a striking increase in the excretion of the sodium ion (Fig. 1) as well as of chloride by the

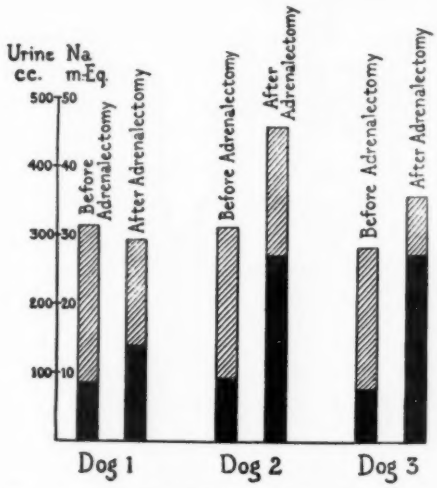

Fig. 2—The effect of adrenalectomy upon the excretion of sodium in relation to urine volume. The total columns represent the daily urine volume and the black columns the daily sodium excretion. The low values following adrenalectomy in Dog 1 result from including the terminal oliguria in calculating the average daily excretion.

kidneys. The loss of base was sufficiently great to indicate that sodium must have come from sources other than the blood stream alone. Not only was the renal excretion of sodium increased after adrenalectomy, but also the concentration of this ion in the urine was augmented despite the fact that the urine volume was greater in the first days after operation than before (Fig. 2). These observations, as well as the later studies of Harrop[14, 15] demonstrated that the decrease in sodium content of the blood in acute adrenal insufficiency is dependent upon an increase in the renal excretion of this ion and not solely upon its internal redistribution. This is borne out by the recent studies of Muntwyler et al[16] who found that, "The outstanding changes of the skeletal muscles of dogs in adrenal insufficiency were a loss of sodium and a gain of water." The lowered concentration of sodium in the blood serum and interstitial fluid following the increased renal excretion of this ion necessitates an osmotic readjustment which, according to Darrow and Yannet[17] and Harrison and Darrow,[18] is reflected by a gain in water limited to the cells. The idea that redistribution of water and sodium, as well as their

excretion, plays a significant part in adrenal insufficiency appears valid from the observations of Harrop,[15, 19] Swingle and his associates,[20, 21] and of Muntwyler et al.[16] The evidence is based upon results obtained when large amounts of cortical extract are given to dogs in acute insufficiency during which both fluid and food are withheld for 24 to 48 hours. Under these circumstances, i.e., when there is no intake of sodium and its excretion is reduced by cortical hormone, there results an increase in the concentration of sodium in the blood serum. It is believed that this increase in serum sodium concentration is due to a shift of interstitial fluid to the blood stream, which results in hemodilution, followed by a more rapid excretion of water than of sodium. It is also believed that a shift of intracellular water contributes to hemodilution and increased water excretion, as well as to the augmentation of potassium excretion in this type of experiment.

After having ascertained that an unusually great loss of sodium takes place through the kidneys following the development of acute adrenal insufficiency, an attempt was made to pursue the mechanism of this disturbance a little further. Despite the fact that ketosis is, as a rule, insignificant in acute adrenal insufficiency and despite the fact that Harrop[22] had found no increase in the lactic acid content of the blood in the adrenalectomized dog, nor we in a patient, it seemed necessary to establish whether or not the presence of some other organic acid might be responsible for the abnormal loss of fixed base. This problem was studied indirectly by determining the titratable acid and ammonia excretion in a patient[23] developing adrenal insufficiency under observation and also by following ammonia excretion in the adrenalectomized dog[24] deprived of cortical extract. In neither instance was an increase observed, as might have been anticipated were an organic acid to be excreted in large amounts. As a matter of fact, ammonia excretion actually decreased slightly with the advance of insufficiency. These observations were considerably extended by Jimenez-Diaz[25] who then explained the loss of sodium on the failure of the ammonia mechanism. This hypothesis does not appear to be tenable because the order of magnitude of the failure of the ammonia mechanism is not great and only becomes manifest relatively late in the development of cortical insufficiency.

In default of direct proof, it is tempting to assume that the increased excretion of sodium in adrenal insufficiency depends upon the loss of the normal power of reabsorption of this ion by the renal tubules. This

will be discussed in detail later.

Intimately related to the disturbances of sodium and water behavior in adrenal insufficiency are abnormalities in the behavior of the potassium ion. Baumann and Kurland,[9] Hastings and Compere,[26] Zwemer,[27] Kendall[28] and others have commented upon the regularity with which, in animals, the concentration of potassium is increased in the blood serum. We observed a similar increase in patients with Addison's disease,[29] but the normal levels were exceeded with perhaps less regularity than in adrenalectomized animals.

From the physiological standpoint, abnormalities in the behavior of the potassium ion appear to bear a mirror image to those of the sodium ion. In contrast to the abnormally increased excretion of the sodium ion, Harrop[14] showed that potassium is retained by adrenalectomized dogs. Subsequently Harrop[30] and Thorn[31] showed that large amounts of cortical extract would increase the excretion of potassium and decrease the excretion of sodium in normal and adrenalectomized animals as well as in human subjects. The retention of potassium in acute adrenal insufficiency is not only demonstrated by its increase in blood serum but also by some increase in the muscle cells as shown by Darrow and his associates.[18] This potassium retention in the cells is associated with an increase in intracellular water. As previously mentioned, the accumulation of water in the cells may, according to Darrow and Yannet,[17] result from the osmotic disturbance initiated by the loss of sodium from the body. The mechanism for the abnormal behavior of potassium, like that of sodium, appears at least in part, to find its origin in the kidney. Thus, Harrison and Darrow[32] have shown that the potassium ion is not concentrated normally by the kidneys of adrenalectomized animals even when they are maintained in good condition by the ingestion of extra sodium chloride. Furthermore, Talbott[33] has recently demonstrated that the potassium clearances of patients with Addison's disease are abnormally low even after prolonged and adequate treatment with desoxycorticosterone esters.

It has been pointed out by Zwemer[27] that adrenalectomized animals are killed by the ingestion or injection of relatively small doses of potassium salts. This observation can be explained on the basis of the lowered excretory capacity for the potassium ion and also by the fact that added potassium has been shown by Harrop,[30] as well as by Wilder and his coworkers,[34] to further the excretion of an already depleted supply of

sodium in the body. Despite the toxicity of potassium salts in the presence of adrenal insufficiency, it seems unlikely that potassium poisoning is the cause of death, at least in patients with Addison's disease. This is indicated by the fact that critically ill Addisonian patients with a marked decrease in serum sodium concentration at times show little or no retention of potassium in the blood serum.

It may be of interest to indicate here one point of difference between the state of dehydration resulting from the loss of base in diabetic acidosis[35] and in starvation ketosis on one hand and that of adrenal insufficiency on the other. In the former states both sodium and potassium excretion are increased, whereas in adrenal insufficiency sodium excretion only is augmented while that of potassium is diminished. This difference may be explained by the specific decrease in the renal clearance of potassium and possibly by decreased gluconeogenesis from body protein due to a loss of cortical adrenal function.

I should now like to comment on other changes in the activities of the kidney in adrenal insufficiency. In 1914, Gaillard[36] and also Porak and Chabanier[37] observed the presence of nitrogen retention and discussed alterations in renal secretion following ablation of the adrenal glands. Swingle suggested in 1933[38] that nitrogen retention develops because of a fall in blood pressure and a decrease in renal blood flow. This view is supported by observations of Margitay-Becht and Gömöri[39] who found marked decreases in creatinine clearance in adrenal insufficiency. Studies of Stahl, Kuhlmann and Urban[40] led to the same conclusion. Talbott[33] has recently made inulin and diodrast clearance studies on a group of Addisonian patients in whom the blood sodium concentration was maintained at a normal level. After treatment with desoxycorticosterone acetate had been continued for many months, these patients still showed disturbances in renal function as manifested by a decrease in the "filtration fraction" which suggested a diminution in efferent arteriolar tone. It seems likely that nitrogen retention and the retention of sulfate and phosphate in marked insufficiency may be in part accounted for by a decrease in renal blood flow or in efferent arteriolar tone. Whether or not the abnormalities of sodium and potassium metabolism and the decrease in ammonia excretion have the same basis is not known. It is possible that they have a more specific basis, i.e., one in which renal cellular function is altered through the lack of one or more substances normally elaborated by the adrenal cortex. For example,

Jimenez-Diaz[25] indicated in 1936 that the rate of deaminization of amino acids by kidney tissue of adrenalectomized animals is less than normal. This has recently been confirmed by Russell and Wilhelmi[41] who suggest that, "the failure of the kidney to deal adequately with electrolytes after adrenalectomy may be related to an underlying failure in the energy-yielding processes of the kidney." This point of view may be extended to include nitrogen metabolism more generally, as Kendall[42] has recently shown that concentrated cortical extract contains a substance other than desoxycorticosterone which lowers the blood urea without increasing sodium retention appreciably.

Regardless of the validity of these concepts, it is clear that a series of profound disturbances appears in the behavior of certain electrolytes and water when the products of adrenal cortical tissue no longer circulate in adequate amounts. It also is clear that these disturbances lead to dehydration, shock and death. It is also certain that the kidney plays an important part in this chain of events. Finally, it is certain that these disturbances can be dramatically corrected in patients with Addison's disease and in adrenalectomized animals by the simple procedure of administering large quantities of sodium salts and water. The same effects can be obtained with large amounts of cortical extract and an adequate supply of salt and water. If the intake of potassium is restricted, as shown by Wilder, Kendall et al,[34] still more gratifying results may be obtained from salt or cortical extract therapy. The similarity of these effects of salt and extract are shown in part in Fig. 3.

One observation has particularly impressed a number of workers interested in adrenal cortical function. When an animal in severe adrenal insufficiency is deprived of food and water, but is given a large dose of cortical extract, striking improvement may take place. This improvement begins before any demonstrable change occurs in the serum sodium, potassium or nonprotein nitrogen or the water content of the blood, i.e., before any obvious redistribution of fluid can occur.[24] This finding makes it apparent that the effect of cortical extract on an animal suffering from acute adrenal insufficiency is not limited to its effects upon electrolyte and water metabolism. In the light of present day knowledge, it seems possible that this immediate response to cortical extract may result from carbohydrate-active steroids in the extract. As long as only extracts of the adrenal cortex and not specific chemical substances elaborated by it were available for study, it was impossible to know definitely whether

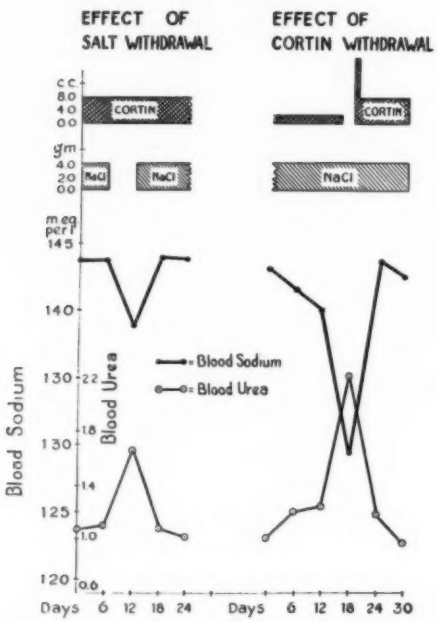

Fig. 3—Comparison of certain effects of the withdrawal of sodium ion from the diet with those of the withdrawal of cortical extract in an adrenalectomized dog, normally maintained with both. The effect upon the serum potassium level parallels that of the blood urea.

the effects on carbohydrate metabolism, the effects on electrolyte metabolism and other effects could all be mediated by one substance or whether different functions were dependent upon differences in chemical structure. In patients with Addison's disease we[29] were unable to demonstrate any correlation between the bouts of hypoglycemia and disturbances in the electrolyte pattern of the blood serum. That is, hypoglycemia occurred when the electrolyte pattern of the blood was entirely normal and conversely, in the presence of severe insufficiency with marked reduction in serum sodium, the blood sugar was usually within normal limits. From these observations it could be surmised but not established that different chemical entities might influence the carbohydrate and electrolyte functions more or less independently.

During the past four years the dissection of the specificity of adrenal cortical functions has been made possible principally by the chemical

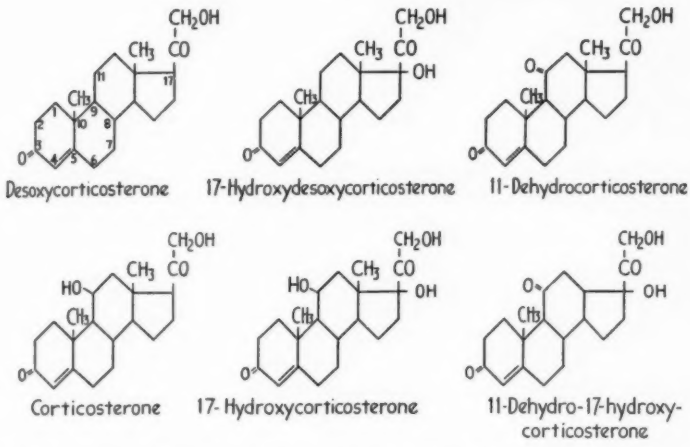

Fig. 4—Steroids with known physiological activity isolated from adrenal cortical tissue.

contributions of Kendall[43, 44] and of Wintersteiner and Pfiffner[45] in this country and of Reichstein[46] in Switzerland. Up to the present time there have been isolated from the adrenal cortex according to Kendall,[42] twenty-four different steroids. Of these six have been shown to possess physiological activity (Fig. 4). These include desoxycorticosterone, 17-hydroxydesoxycorticosterone, corticosterone, 11-dehydrocorticosterone, 17-hydroxycorticosterone and 11-dehydro-17 hydroxycorticosterone known as compound E of Kendall. How many of the steroids isolated from adrenal cortical tissue occur naturally and how many may appear as degradation products is not yet known. One of the cortical steroids namely desoxycorticosterone, was synthesized by Steiger and Reichstein[46] in 1937 and since that time its effect upon adrenal insufficiency has been extensively studied.

In England, Levy Simpson[47, 48] first observed the clinical improvement of Addisonian patients following both the subcutaneous injection and implantation of pellets of desoxycorticosterone acetate. In this country, Thorn and his associates[49, 50, 51] were the first to make similar but much more extensive studies both upon adrenalectomized dogs and upon patients with Addison's disease. Our own clinical studies*[52, 53] were en-

* All desoxycorticosterone and corticosterone used in our studies has been furnished through the courtesy of Roche-Organon, Inc., Nutley, N. J.

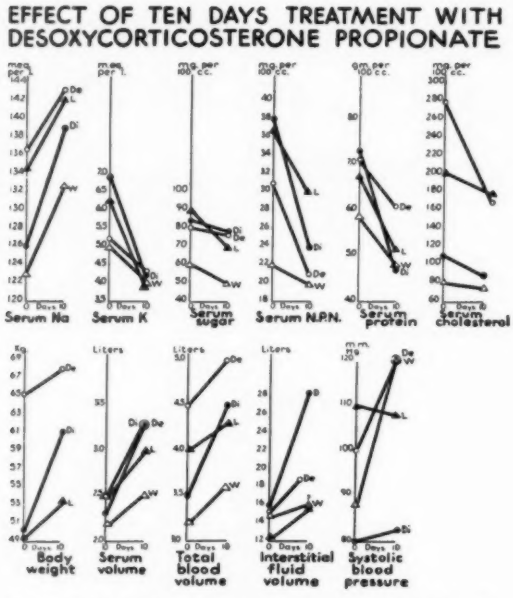

Fig. 5—Effects observed as a result of the administration of an average daily dose of 19 mg. of desoxycorticosterone propionate over a period of 10 days in patients with Addison's disease.

tirely confirmatory of Thorn's. It has become clear that the administration of desoxycorticosterone esters has the same qualitative effects upon water and electrolyte metabolism in adrenal insufficiency as does the administration of either large doses of sodium salts or large doses of the available commercial cortical extracts given in conjunction with salt and water. The magnitude of the effects of even small doses of desoxycorticosterone is much greater than can be obtained by the use of salt or of cortical extract.

The results of desoxycorticosterone treatment in patients with Addison's disease are now well known and can be briefly summarized (Fig. 5). The esters of this steroid cause striking retention of salt and water. The rate of retention of the sodium ion usually exceeds that of water so that, as a rule, the serum sodium concentration rises to normal and is maintained at a normal level as fluid retention continues. In some instances, however, water is retained more rapidly than sodium so that the sodium concentration of the blood serum may actually fall during

the first days of treatment. The amount of salt and water retained varies greatly in different patients and cannot be correlated with the initial serum sodium or protein concentration or with the initial plasma volume or with the severity of the disease. For example, one of our patients gained 11 kilos in the first 10 days of treatment with an average daily dose of 19 mg., and became markedly edematous. Another patient whose disease appeared to be equally severe gained but 2 kilos in 30 days with an average daily dose of 24 mg. The retention of salt and water is reflected by an increase in interstitial fluid volume as well as by increases from 300 to 1200 cc. in plasma volume in the first 10 days of treatment.

Potassium metabolism, like that of sodium, is profoundly influenced in adrenal insufficiency by desoxycorticosterone. Thus, the concentration in the blood serum is not only reduced to normal, but has been observed in some of our patients to fall as low as 2.4 m.eq. per liter. The urinary excretion of potassium increases regularly on the first day or two of hormone injection and thereafter becomes variable.

Disturbances of renal function, as measured by nitrogen retention and failure of ammonia excretion, are influenced within the first 24 hours of desoxycorticosterone administration. The recent studies of Talbott,[33] already mentioned, indicate, however, that the improvement in renal function brought about by desoxycorticosterone is not maintained at a normal level over long periods of time despite adequate dosage of hormone, i.e., enough to maintain normal serum values for sodium and potassium.

The effect of desoxycorticosterone esters upon arterial blood pressure in patients is worthy of comment. The pressure gradually rises to normal in the course of 2 to 4 weeks of treatment, as it tends to do in patients treated with salt alone. This slow recovery stands out in contrast to the almost immediate effects upon water, electrolyte metabolism and renal function. In a number of instances, the blood pressure of patients treated with desoxycorticosterone esters has exceeded normal limits and has been observed to be 175/110, 160/92, 154/105 and 146/108 in different patients. The mechanism of this hypertension is not understood but a comparison of the effects of desoxycorticosterone and salt in one patient is of interest. In this patient, whose pressure reached 175/110 with desoxycorticosterone, crises with a fall in sodium and fall in pressure to 85/60 were induced on two occasions by the withdrawal of salt from the diet. When salt was given in doses of 15 grams daily

without any cortical hormone, the blood pressure rose to 160/100. At autopsy this patient was found to have marked renal arteriolar sclerosis and both adrenal glands were replaced by tuberculous masses. In this individual whose adrenal function was so seriously impaired that, without salt or desoxycorticosterone, he sank into profound hypoadrenalism, hypertension could be induced, in the presence of renal arteriolar disease, by the administration of either sodium chloride or desoxycorticosterone. Swingle[54] has recently suggested that the elevation of arterial pressure in adrenalectomized dogs treated with desoxycorticosterone results from an increase in arteriolar and capillary tone. In view of the fact that a similar effect on blood pressure may result from salt alone, the question must be raised whether this increase in pressure may not be more properly ascribed to an ion effect on the vessels than to direct hormone action.

The mechanism of pigmentation in Addison's disease remains obscure and the effect of desoxycorticosterone upon it is still equivocal. Thorn[55] has maintained that treatment with this steroid decreased pigmentation. We have felt that decrease in skin color might be ascribed entirely to rehydration and gain in weight. The recent disappearance of "ink spots" from the buccal mucous membrane in one of our patients treated for two and a half years, perhaps, tends to support the viewpoint of Thorn.

Early in the course of our experience[52] it was found that whereas the subjective and objective benefits derived from treatment with desoxycorticosterone esters are impressive, this therapy is not devoid of danger. Indeed, five patients developed symptoms and signs of congestive heart failure including pulmonary congestion, elevation of venous pressure and cardiac dilatation as is shown in Fig. 6. The mechanism of this cardiac failure was not determined but did not appear to be directly correlated with the degree of increase in plasma volume, the height of the arterial pressure attained or the degree of depression of the serum potassium level.

Because of the development of this complication with large doses of desoxycorticosterone, it seemed appropriate to study[56, 57] the effects of prolonged administration of this steroid on normal animals. For this purpose, a series of dogs was given 25 mg. of desoxycorticosterone acetate daily for a period of some weeks. Although we were unable to produce either edema or cardiac dilatation in these animals, nevertheless two striking abnormalities appeared with great regularity. The ani-

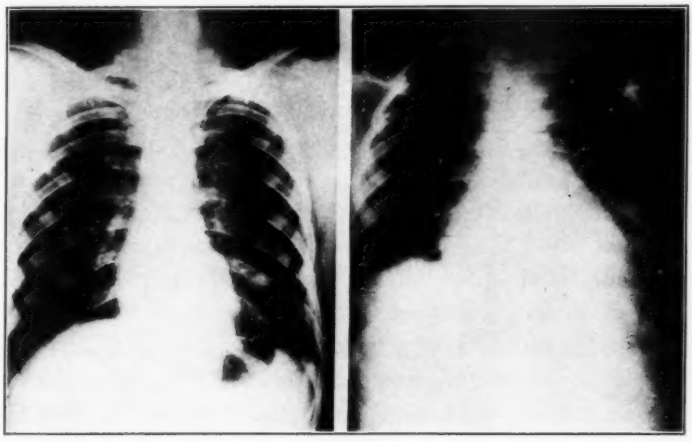

Fig. 6—The effect of desoxycorticosterone upon the heart of a patient with Addison's disease. At the left is the heart before treatment. At the right is the heart after treatment with excessive doses.

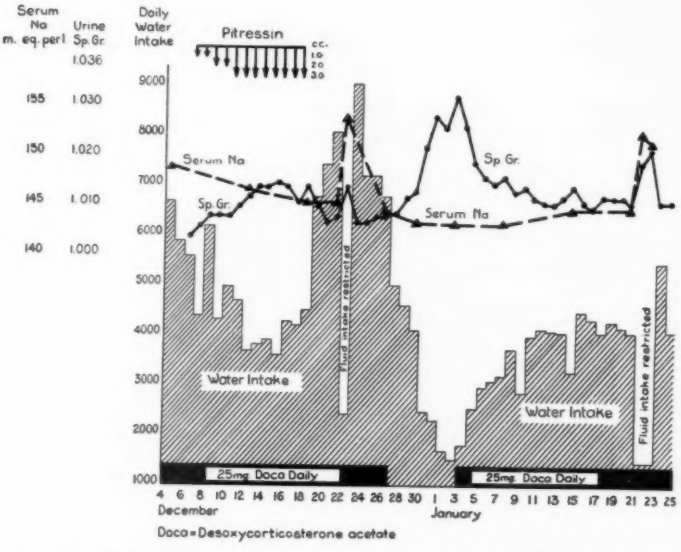

Fig. 7—"Diabetes insipidus" induced in a normal dog by daily injections of desoxycorticosterone. The urine output corresponded to water intake and the weight of the animal remained constant.

mals, in the course of 10 days, began to increase their water intake and output and gradually developed a diabetes insipidus-like syndrome. The degree of water drinking was increased by the addition of sodium chloride to the diet. The fluid intake increased from 500 cc., as a rule, to about 3-5 liters a day and the urine volume increased correspondingly. Part of the record of water-drinking of one dog is shown in Fig. 7. The water intake appeared to be slightly depressed by the injection of pitressin and this change was accompanied by an increase in the specific gravity of the urine. The restriction of fluid was associated with a sharp rise in serum sodium level. Unlike true diabetes insipidus, the restriction of fluid intake was associated with an increase in urine specific gravity. The "diabetes inspidus" was promptly terminated by the discontinuation of desoxycorticosterone injections. Thus, the urine specific gravity rose and the water turn-over dropped to normal, even though the sodium intake was kept at a constant level.

The second abnormality which developed in the normal dogs treated with desoxycorticosterone was a curious type of muscle weakness. This began to develop 4 to 5 weeks after the onset of treatment. In the early stages it appeared as intermittent periods of weakness. In these attacks it was impossible for the animals to raise their heads and weakness of the extremities, particularly the hind legs, was marked. These attacks of weakness usually occurred in the afternoon, possibly bearing a relation to the time of feeding, and would disappear by the following morning. In the course of about 10 days to 2 weeks, the weakness became progressively worse and more continuous. If not treated, the animals would finally succumb.

The blood serum of these animals developing "diabetes insipidus" and periodic muscle weakness showed an increase of 4 to 8 m.eq. per liter in sodium and a depression of potassium to about 2.5 m.eq. per liter.

It was found[58] that if the animals were given a 0.15 per cent solution of potassium chloride to drink instead of tap water, the development of muscle weakness did not occur, but no influence was observed upon the development of the "diabetes insipidus." The substitution of tap water for potassium chloride solution led to the appearance of intermittent muscle weakness in about 10 days. It was found that the administration of potassium chloride tended to prevent the decrease in serum potassium level, but had no influence on the elevated sodium concentration.

Analysis of the skeletal muscles of animals with severe weakness

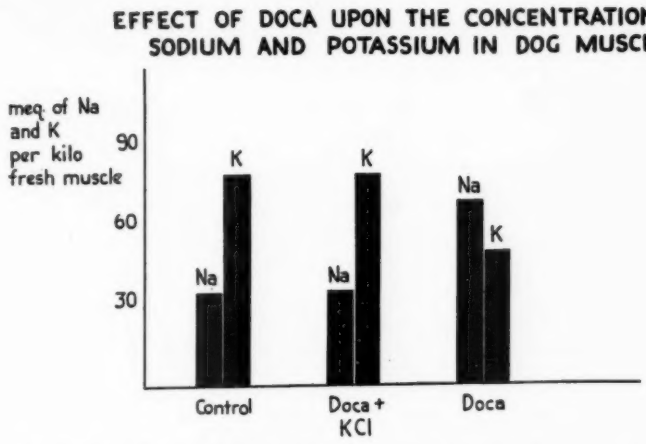

Fig. 8—The effect of desoxycorticosterone acetate upon the concentrations of sodium and potassium in the skeletal muscle in the dog. N.B. The addition of KCl to the drinking water inhibited the muscle changes but had no effect upon the "diabetes insipidus."

showed that they contained a large amount of sodium and less than the normal amount of potassium. Similar changes had been described by Darrow[59] in the muscles of rats treated with desoxycorticosterone. The increase in muscle sodium was found in our studies[58] to be prevented when potassium chloride was added to the drinking water as is shown in Fig. 8. Analysis of the muscles for nitrogen, chloride and water in paralyzed animals and animals protected with potassium chloride indicated no apparent change in the extracellular water jacket or so-called chloride space. This is demonstrated in Fig. 9. In Fig. 10 it is shown that the intracellular replacement of potassium by sodium appeared to be on an approximately 1 to 1 basis, an atom of sodium being gained for each atom of potassium lost.

In these studies it is clear that the "diabetes insipidus" could be correlated with an increase in sodium concentration in the serum and therefore in the extracellular fluid. This elevation in sodium level and the "diabetes insipidus" persisted regardless of potassium chloride administration. The muscle weakness, on the other hand, was associated with an increase in intracellular sodium. This change could be prevented by potassium chloride feeding even though the serum sodium concentration remained elevated. It thus seems preferable to speak of the effect

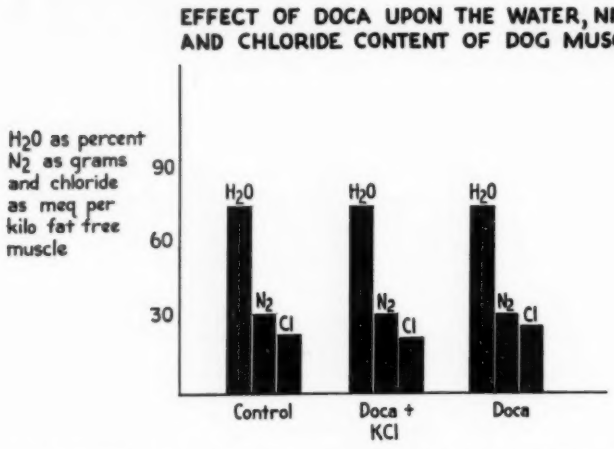

Fig. 9—Analyses of muscles of normal dogs receiving large doses of desoxycorticosterone yield no evidence of an increase in interstitial fluid, i.e., the "chloride-space."

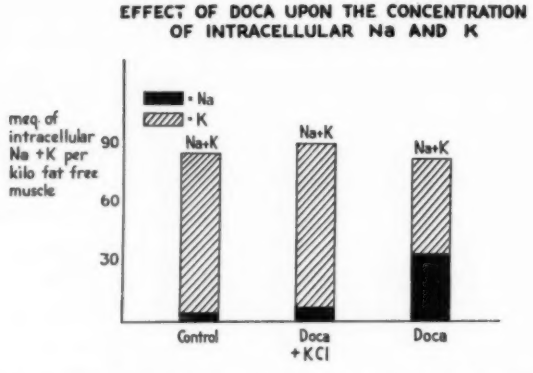

Fig. 10—The intracellular replacement of the K ion by the Na ion in muscles of normal dogs receiving desoxycorticosterone is on an approximately 1 to 1 basis. This replacement of K by Na is inhibited by the administration of KCl.

of desoxycorticosterone upon intracellular electrolytes in the normal dog as one in which potassium lost from the cells is *replaced* by sodium rather than one in which a high concentration of extracellular sodium in some way *displaces* intracellular potassium. In other words it appears that sodium goes into muscle cells only when potassium comes out. This view is consistent with the idea that desoxycorticosterone, by in-

creasing the renal excretion of potassium, lowers the serum potassium concentration and shifts the equilibrium between intracellular and extracellular potassium in the direction of an increased loss of potassium from the cells. Heppel's[1] observations on the increase in intracellular sodium in rats raised on a low potassium diet offer support for this interpretation. It seems clear therefore, that when the available supply of potassium is reduced either by reduction in intake or by excessive excretion sodium replaces the potassium which is lost from the muscle cells.

These effects of excessive doses of desoxycorticosterone in normal dogs bear some similarity to electrolyte disturbances observed first by Anderson[60] in the blood serum of patients suffering from Cushing's syndrome. In these patients, in whom tumor of the adrenal cortex is often present, there may be an elevation of serum sodium and depression of potassium. Whereas mild diabetes insipidus has been reported in these patients[61] this has not been observed in the small group of cases studied by us. Furthermore, muscle biopsy carried out in three of our cases has not revealed the replacement of potassium by sodium seen in dogs treated with desoxycorticosterone. The muscle weakness of patients with Cushing's syndrome does not, therefore, appear to have the same chemical basis as does the intermittent paralysis of desoxycorticosterone treated dogs.

I have dealt at length with the action of desoxycorticosterone esters upon electrolyte metabolism. I should like now to consider briefly the effects of the various physiologically active steroids isolated from the adrenal cortex upon the interrelations of electrolyte behavior, life maintenance, carbohydrate metabolism and the capacity for muscular work. In general there appears to be a close parallelism between the effect of a steroid on sodium retention and on life maintenance. This is demonstrated by the fact that sodium salts in the absence of cortical hormone will sustain adrenalectomized dogs and rats. There is also an apparent correlation between the effects upon carbohydrate metabolism and upon work-capacity. Furthermore there appears to be a possible antagonism between these two groups of functions. Most of the studies devoted to the correlation of these various activities have had to be carried out on animals and are unfortunately limited in number because of the small quantities of those steroids so far isolated and because only desoxycorticosterone has been made available through its synthesis.

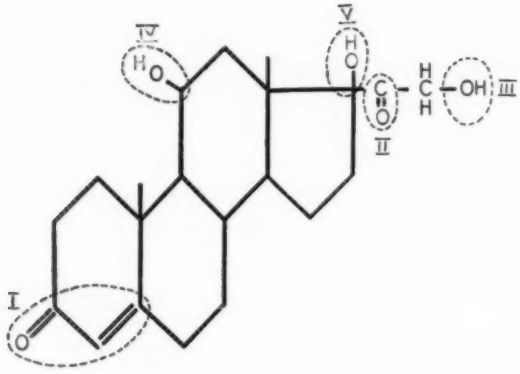

Fig. 11—I. Is essential for all known physiological activity. II. is essential for all known physiological activity. III. enhances sodium retention; necessary for carbohydrate activity. IV. (Either a hydroxyl or a carbonyl group.) In the presence of III, decreases sodium retention and increases carbohydrate activity. V. In the presence of III, and ? IV, increases carbohydrate activity and induces sodium excretion. This correlation of adrenal function and structure of various steroids is suggested by Thorn. (Reprinted with permission.)

The great advances in our understanding of carbohydrate activity have developed primarily from the studies of Britton and Sylvette,[62] Kendall and his associates,[28,63] C. N. H. Long[64] and from Thorn and his co-workers[65] in the past 10 years. The relation between the capacity for muscular work and the various cortical steroids has been clarified through the carefully controlled observations of Ingle.[66] It is established that desoxycorticosterone is the most potent of the isolated adrenal steroids in affecting sodium retention and life maintenance. Yet this steroid in man, as well as in the experimental animal, is virtually without effect upon carbohydrate metabolism or work-capacity, the latter being determined in adrenalectomized rats. Corticosterone has definite but less sodium-retaining effect in man[67] and animals[51] than has desoxycorticosterone. On the other hand it has slight but demonstrable effect upon carbohydrate metabolism in man.[65,67] In animals it has considerably greater effect upon carbohydrate metabolism and work-capacity than has desoxycorticosterone.

Very recently Thorn[68] has made a most important advance in our knowledge. He has shown that 17-hydroxycorticosterone and 11-dehy-

dro-17-hydroxycorticosterone (compound E of Kendall), the two steroids most active in their effects on carbohydrate metabolism and work-capacity, have no sodium retaining effect in the dog. Moreover they appeared to increase the excretion of the sodium ion. This fact is the more interesting since the effect of these steroids on life maintenance is indeed relatively small. On the basis of these observations, Thorn has presented a diagram (Fig. 11) in which he has attempted to correlate the relation between various physiological activities of the cortical steroids and their chemical structure.

Before closing I should like to mention evidence suggesting that adrenal cortical insufficiency may be associated with significant physiological disturbances other than those of electrolyte and carbohydrate metabolism. To what extent some of these changes may be primary and specific in nature and to what extent they are secondary to the recognized disturbances and make their appearance because the organism is "sick" is at times difficult to determine. For example, in our laboratory we have found that some degree of tetrabromphenol-sulfonephthalein retention was present in 12 of 16 patients with Addison's disease. This retention varied from 5 to 15 per cent at the end of one half hour and was not related to the severity of sodium loss. This constitutes but slight retention of the dye, but is more than is normally encountered. Similarly a mild depression of the basal metabolic rate is found in Addisonian patients as it is in adrenalectomized animals. Whether this results from a specific depression of thyroid activity from lack of adrenal hormone or whether it may possibly result from decreased blood flow or other causes is not known. The failure of glucose and fat absorption from the bowel of animals in adrenal insufficiency was thought by Verzar[69] to signify that a specific failure of phosphorylation existed in adrenal insufficiency. It was shown, however, by Althausen, Anderson and Stockholm[70] that the failure of absorption of glucose was dependent only upon dehydration and that administration of saline solution restored glucose absorption to normal. MacKay[71] also found that fat is normally absorbed if salt solution is given to avoid dehydration.

In 1933 Swingle[38] and his coworkers first suggested the possibility that the adrenal cortex exerts an effect upon the capillaries and that loss of the adrenal cortex resulted, for this reason, in the state of shock. Since that time a large number of studies have been devoted to the possibility of a relation between the adrenal cortex and the cause and cure

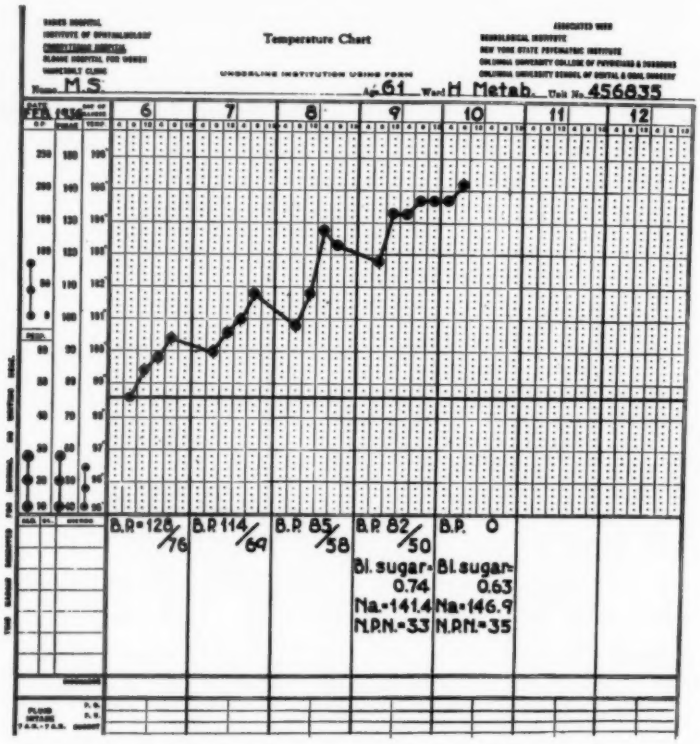

Fig. 12—A fatal adrenal crisis occurring without significant disturbance of the electrolyte pattern of the serum or of the blood sugar. No cause of death other than destruction of the adrenal glands was found post mortem.

of shock. This interest has been greatly augmented recently for obvious reasons, but no final answer can as yet be given. The evidence concerning the influence of adrenal cortical hormones in the treatment of experimental and clinical traumatic shock is at present controversial and not wholly convincing. Menkin's[72] observation that the administration of cortical extract prevents the usual capillary dilatation following the injection of leukotaxine, however, is suggestive. The recent observation of Swingle[34] that plasma transfusion in a dog in adrenal insufficiency causes edema and collapse whereas this can be prevented if the dog is first treated with desoxycorticosterone or cortical extract also indicates a capillary disturbance in adrenal insufficiency.

We pointed out four years ago[29] that a certain number of patients

with Addison's disease die a typical Addisonian death, characterized by profound asthenia, falling blood pressure, a small or soft pulse and peripheral cyanosis but without the characteristic chemical changes in the blood serum. In these patients, the syndrome of shock may develop rapidly and without apparent relation to the state of the electrolyte and water metabolism or to the blood sugar level, but it is associated with a terminal rise in temperature which cannot be explained at autopsy (Fig. 12). Furthermore, in recent years, it has been found that these patients, at times, fail to respond to the administration of adequate therapy with desoxycorticosterone and potent cortical extract as judged by their effects on the water content of the blood plasma, the concentration of serum electrolytes and the blood sugar. It has been our impression that these patients die from a disturbance in vasomotor regulation, either peripheral or central in origin and that this is not consistently controlled by the cortical hormones now available.

In conclusion it may be stated that the adrenal cortex has been shown to exert an important influence upon the physiological activity of certain electrolytes and water as well as upon carbohydrate metabolism. Furthermore, through the chemical identification of a number of steroids isolated from the adrenal cortex an encouraging beginning has been made in the correlation of the chemical structure of these substances with certain physiological activities. It is to be hoped that with the further advance of our chemical knowledge of the hormones of the adrenal cortex that their effects upon capillary tone and permeability as well as upon cellular metabolic processes in general will be further elucidated.

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WALTER LINDSAY NILES
1878-1942

WALTER LINDSAY NILES

An Appreciation

In the death of Walter Lindsay Niles The New York Academy of Medicine has suffered an irreplaceable loss. Dr. Niles was born on January 2, 1878 on one of the farms of the community known as "Niles Settlement," founded in 1808 in the Town of Lebanon, N. Y., by his great, great grandfather (Nahum Niles) and his sons, and there both his father, Isaac Newton Niles, and his mother, Harriet Lois Lindsay, were also born.

His paternal ancestor in America was John Niles who arrived from England on the ship Speedwell and settled in Dorcester, Massachusetts in 1634. His maternal ancestor came to this country from Scotland in 1645.

Dr. Niles was of the ninth generation descended from John Niles. This then is the foundation upon which his character was built. No wonder he possessed great courage, common sense to a high degree, a perfectly educated will and honesty of purpose. Virtue and genius were in his blood.

In his early boyhood he attended the district school in Lebanon. He graduated from the High School at Norwich, N. Y. in 1896 and in the autumn of that year entered the School of Civil Engineering, Cornell University, with the aid of a scholarship won in competitive examination.

With the death of his father in 1898, Dr. Niles decided not to complete his engineering course but to enter the school of medicine.

During his school-boy days, Walter Niles commanded the respect and affection of his companions and even his elders in the community recognized in him the leader and representative of his age group on any matter affecting policy. As an undergraduate in Cornell he rowed on the freshman crew squad and sang on the glee club. He was the chairman of a committee which published the "Songs of Cornell" and was a member of his senior banquet committee. He was a member of Sphinx Head, a senior honorary society, and of Savage Club.

After his graduation from medical school in 1902 he served two

years as a member of the intern staff of Bellevue Hospital. One of the attending physicians on the medical service at this time was the then Professor of Medicine at Cornell, Dr. Gilman Thompson, and it was he who persuaded Dr. Niles, after he had finished his internship in 1904, to remain in New York to take up the practice of medicine. From the day this decision was made down to the time of his death, he devoted himself to every phase of medical care and served humanity with great distinction to himself and to his profession.

Very shortly after the completion of his internship, he was appointed to the attending staff of Bellevue Hospital as an adjunct assistant attending physician. Later he became a consulting physician to this institution. He was also consulting physician to the Memorial Hospital, the New York Infirmary for Women and Children and the Southampton, Jamaica and Nassau Hospitals. He was an attending physician to the New York Hospital and a member of the Joint Administrative Board of The Society of the New York Hospital and Cornell University Medical College. He was professor of Clinical Medicine in the Medical College for many years. He was not only an inspiring teacher but his capacity for organization led to his being appointed Dean of the College in 1919, an office he retained for nine years. Indeed, due to the illness of Dean Ladd, he was serving as acting Dean at the time of his death.

In 1908 Dr. Niles was elected a Fellow of The New York Academy of Medicine. During his more than thirty years of Fellowship he served on the following committees of the Academy: Admissions, Public Health Relations, Medical Education, Problems of Medical Practice, Professional Standards, Fund Raising and finally he was Chairman of its Board of Trustees and the Executive Committee of this Board.

He declined an invitation to become President of The New York Academy of Medicine because other duties to which he was already pledged would not give him sufficient time to do this office full justice.

Dr. Niles was a member of numerous scientific societies and organizations among which were: The Association of American Physicians, The American Climatological and Clinical Association, The Harvey Society and The Practitioners Society. His clubs were The Links, Century Association, Cornell, National Golf Links, Shinnecock Hills Golf Club, Meadow Club (Southampton), Piping Rock and Deepdale.

In the very early days of the first World War Dr. Niles received

a telegram from Dr. Theodore Janeway offering him a commission as major in the United States Army Service Medical Corps.

He was persuaded, against his own wishes and desires, that he could best serve his country by retaining his teaching post in the medical school. Once he was convinced of this he made the sacrifice cheerfully.

Dr. Niles was as successful in private practice as he was in every other phase of medicine with which he was identified. People liked him and he liked people. I heard one man give the following reason for his success in the practice of medicine, "People felt safe in his hands." That statement is substantial evidence that his good judgement and wisdom were associated with high character, objective, straight thinking and complete honesty, blended with kindliness, gentleness, patience and tolerance.

One of the reasons why he did so many things well was that he possessed the rare quality of being able to do one thing at a time to the exclusion of all else. When he played, and he loved to play, he concentrated on play. When he worked, all his thought was centered on the single problem in hand.

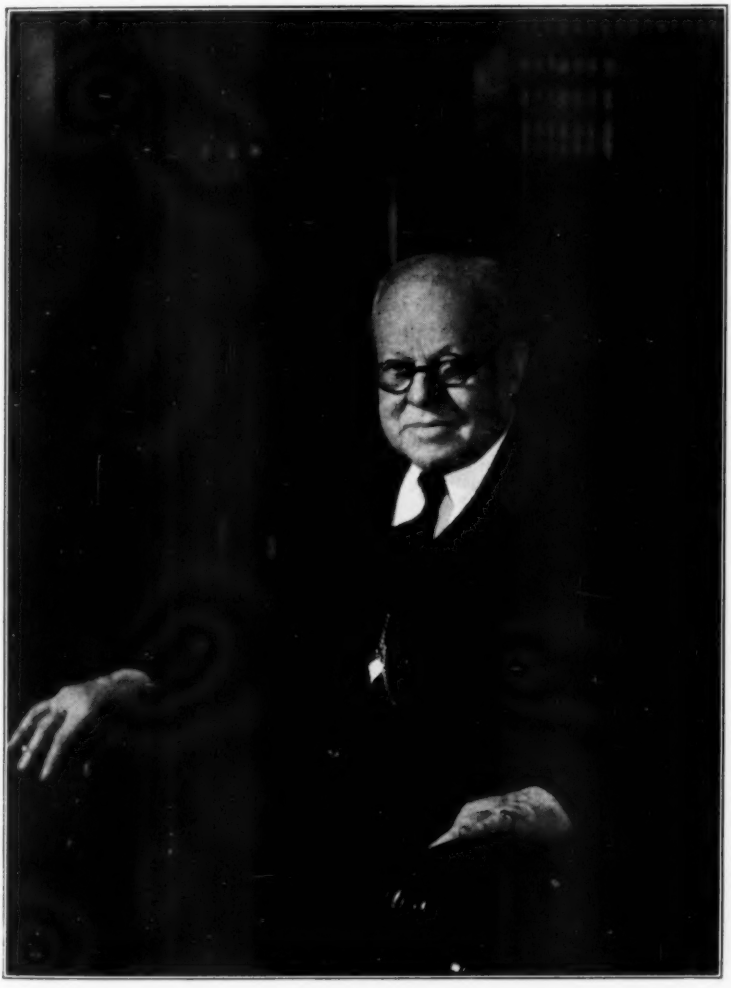
On May 20th, 1908 he married Louise Vezin, daughter of Charles Vezin and Adah Delamater.

There were four children of this marriage: John Lindsay Niles, Charles Lindsay Niles, Harriet Lindsay Niles–now Mrs. Edward A. Hurd, Jr.–and Nelson Robinson Niles. The latter two children and his wife survive him.

Schiller said: "Genuine morality is preserved only in the school of adversity." There was plenty of adversity in Walter Niles' life and in every instance when he was compelled to face ill fortune, he did so with a decision and nobility that was characteristic of him. He refused to be crushed. He carried on with a fine sense of his obligation to the world. Whatever concerned humanity concerned him. He refused to permit Fate to destroy him until she did a complete job of it. He loved life but only a life capable of doing things.

His death came with the suddenness he would have wished and it came at the very zenith of his career.

MALCOLM GOODRIDGE.



SAMUEL W. LAMBERT
1859-1942

SAMUEL W. LAMBERT

DR. SAMUEL W. LAMBERT died February 9th, 1942 in his eighty-third year. His life was one of action and accomplishment. A wonderfully successful practitioner, an educator, bibliophile, fisherman and delightful companion, he gave all he had, and that was much.

His father, Dr. Edward W. Lambert said all he could give his children, of whom eight grew to maturity, was a good education. Dr. Lambert had that, and made the most of it. He received his A.B. from Yale in 1880, and his Ph.B. after two additional years at the Sheffield Scientific School in preparation for his medical studies. At P. & S. his preceptor was Dr. H. B. Sands, and he was graduated in 1885 with Harsen honors. He received an appointment at Bellevue and then studied abroad for two years. He started practice in New York, in 1889.

From the very beginning he was much interested in Medical Education. Impressed with the woeful lack of practical obstetrical teaching in this country, with Dr. James W. Markoe, and with the backing of his father, Dr. Thomas M. Markoe, Dr. William T. Lusk, and Dr. William M. Polk, he organized the New York Midwifery Dispensary in Broome Street, in 1890. Students were enrolled, and after preliminary instruction, under supervision they delivered women in their tenement homes. During its two years of independent existence, over 300 students took the course. So successful and valuable was this work that the Society of the Lying-In Hospital was roused from a long period of inactivity. Originally organized as a hospital, it had degenerated into an eleemosynary organization giving deserving women $25 to pay for their confinement. The Trustees founded a hospital at 17th Street and Second Avenue, which opened in 1895. They took over the Broome Street organization as its out-patient department in 1892. Dr. Lambert and Dr. Markoe were therefore responsible for starting a service well-remembered by the older members of the profession, and which did much in developing medical education. Dr. Lambert served on the Attending Staff of the Lying-In for twelve years.

In 1904 he became Dean of the College of Physicians and Surgeons, and for fifteen years devoted his energies to improving the scope and

character of the teaching in that organization, in spite of much opposition. He brought about its union with the Presbyterian Hospital and formed plans, never entirely carried out as he planned them, for the development of a teaching hospital, in which emphasis was laid on the teaching of practical medicine to every student in the College through bedside experience. Retiring in 1919, he was made its first Dean Emeritus.

As a practitioner of Medicine, Dr. Lambert was eminently successful, building up a large private and, later, consulting practice. Always abreast of the times, he was wise and resourceful, never forgetting the comfort of his patients in his interest in their diseases. He was one of that fast diminishing number of physicians who treat *patients* and not *cases*. His sympathy for the suffering or sorrowing was very real. His patients were devoted to him and became his fast friends and admirers. As a consultant, he was considerate and helpful to younger men, and when in difficulty they frequently called on him for help. They not only respected and admired him, but to many, he was "Dr. Sam."

Dr. Lambert was connected with many hospitals and medical societies. The long list need not be repeated here. In addition to the Lying-In, he was at various times Attending Physician to the Nursery and Childs, New York and St. Luke's. With the latter he was actively connected for twenty-three years. He was Consulting Physician to more than twenty institutions. The Medical Societies to which he belonged, both national and local, were also many—the Association of American Physicians, the College of Physicians, the Practitioners and others. Just before Sir William Osler left this country, he invited a small group of physicians and surgeons to form with him the Interurban Medical Club. Dr. Lambert was one of them.

Although elected a Fellow of the Academy in 1891, his deep interest in it was not shown until he became President in 1927. He did much in those important years to develop its ever-widening sphere of usefulness to its members and to the public. His valuable services continued after his term of office was over. He was particularly interested in the Library, for books were one of his hobbies. The assembling of the collections for the Rare Book Room and its stacks, including the purchase of the Streeter Collection, was largely due to his efforts and enthusiasm. Always interested in Vesalius and his Anatomy, he stimulated a further search in Munich for the original woodblocks, resulting

in the discovery of many which had been lost up to that time. He collected the money necessary to issue an Atlas containing all the original illustrations, beautifully printed on modern paper by modern methods. He was a very active member of the Library Committee from 1932 to 1941, when he was made Consultant. His interest and support never flagged. He was made a Benefactor of the Academy in 1941.

Dr. Lambert's life was a broad one. He played as actively as he worked—when he had the time. An enthusiastic bibliophile, he collected the books he loved, and he knew them from cover to cover. He was a regular attendant at the meetings of the Grolier and Charaka Clubs. To hear him talk about his beloved volumes was a rare treat. His little book "When Mr. Pickwick went Fishing" illustrates his wide knowledge of his hobby. An ardent fisherman himself, his collection of editions of Isaac Walton's "Compleat Angler" and Cotton's works is a notable one and was probably his most treasured possession. He collected them for many years, and each new acquisition gave him great joy. He belonged to several fishing clubs in this country and in Canada.

Dr. Lambert was a loyal friend, and a companion who from the store of his exceptional memory of men and events, told anecdotes, apt and to the point, tinged with rare humor, demolishing chicanery and fraud which he hated.

He led an active, constructive, worth while life. He will be sadly missed.

PHILIP VAN INGEN.

DEATHS OF FELLOWS

LAMBERT, SAMUEL WALDRON: 101 East 72 Street, New York City; born in New York City, June 18, 1859; died in New York City, February 9, 1942; received from Yale University the degree of A.B. in 1880, Ph.B. in 1882, A.M. in 1905; and from Columbia University the degree of D.Sc. in 1921; graduated in medicine from the College of Physicians and Surgeons in 1885; elected a Fellow of the Academy February 5, 1891; served the Academy as its President from 1927 to 1929, as a member of the Board of Trustees from 1929 to 1939, as a member of the Committee on Public Health Relations from 1929 to 1936, as a member of the Committee on Library from 1932 to 1942 and as consultant to that Committee from January 1942 to the time of his death.

Dr. Lambert was dean emeritus of the College of Physicians and Surgeons, Columbia University, having served as its dean from 1904 to 1919. From 1903 to 1919 he was professor of clinical medicine at that institution. He was consulting physician to St. Luke's, New York, Presbyterian, St. Vincent's, Neurological Institute, New York Orthopedic, Ruptured and Crippled and St. John's, Riverside and Yonkers Hospitals. He was a member of the Board of Trustees of Roosevelt Hospital (1904-19), a Fellow of the American College of Physicians, a member of the Association of American Physicians, the American Gastro-Enterological Association and the State and County Medical Societies.

WALSH, JAMES JOSEPH: 344 West 72 Street, New York City; born in Archbald, Pennsylvania, April 12, 1865; died in New York City, March 1, 1942; received the degree of A.M. from Fordham University in 1885, Ph.D. in 1889, LL.D. from Georgetown University in 1901, and Sc.D. from Notre Dame in 1909; graduated in medicine from the University of Pennsylvania Medical School in 1895; elected a Fellow of the Academy March 3, 1904.

Dr. Walsh became an instructor in medicine in 1900 at the New York Polyclinic School of Medicine and adjunct professor in 1904. The latter position he resigned in 1907 to become the acting dean and professor of physiological psychology at Cathedral College. He was consulting physician to Gabriels Sanatorium and St. Vincent's Hospital, a Fellow of the American Medical Association, a member of the American Association for the Advancement of Science, and a member of the State and County Medical Societies.

Dr. Walsh was a prolific writer on medical, scientific and religious subjects and established the Fordham University Press which published his articles on the history of medicine and related subjects.

WITT, DAN HITER: 71 East 71 Street, New York City; born in Charlottesville, Virginia, May 20, 1890; died in New York City, February 15, 1942; graduated in medicine from the University of Virginia in 1914; elected a Fellow of the Academy October 2, 1924.

Dr. Witt was instructor in medicine at Cornell University Medical College, assistant visiting physician to the New York Hospital and consultant visiting physician to the Manhattan Eye, Ear and Throat Hospital. He was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association and a member of the State and County Medical Societies.

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